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THE ABSORPTION OF RADIOPAQUE SUBSTANCES USED IN HYSTEROSALPINGOGRAPHY*†‡

A Comparative Study of Various Aqueous and Oily Media

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THERE are many reports in the literature on the persistence of various radiopaque substances in the pelvis for extended periods following hysterosalpingography, and several have contained unfavorable comments on certain media. Ries[9] and Lash[5] have stressed the foreign-body effects and resultant encysted masses produced by Lipiodol. Rubin[11] has corroborated these findings. Signs of peritoneal irritation and serious pelvic complications have been recorded by Flew,[3] Rubin,[12] Brun and Cortesi,[2] Lecerne and Béclère,[6] and Sicard and Solal.[14] The escape of Lipiodol into the utero-ovarian venous system with resultant pulmonary emboli has been reported by Zacharin,[17] Walther,[16] Lin and Tsou,[7] Roblee and Moore,[10] and Ingersoll and Robbins.[4]

Newer substances[1, 8, 13, 15] evolved in the last decade are said to overcome the objections to the slowly absorbed oil media by virtue of their physical properties and rapid absorption.

A study of the clinical suitability and absorbability of five radiopaque media was made to obtain information which might assist in selecting the most desirable agent. The present paper reports data obtained in the study of 118 cases.

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Materials and Methods

The following currently used commercial radiopaque media were used*: Rayopake, Skiodan, Lipoidol, Iodochlorol, and Lipoiodine. The patients studied were selected from the Gynecologic Service of the University Hospital.

Altogether 200 women were subjected to hysterosalpingography. Absorption studies were conducted on 118 of these patients and are reported here. Thirty-eight of these patients subsequently were subjected to laparotomy for gynecologic disorders, and their pelvic tissues were studied for gross and microscopic evidence of inflammatory reaction. These results are being reported separately.

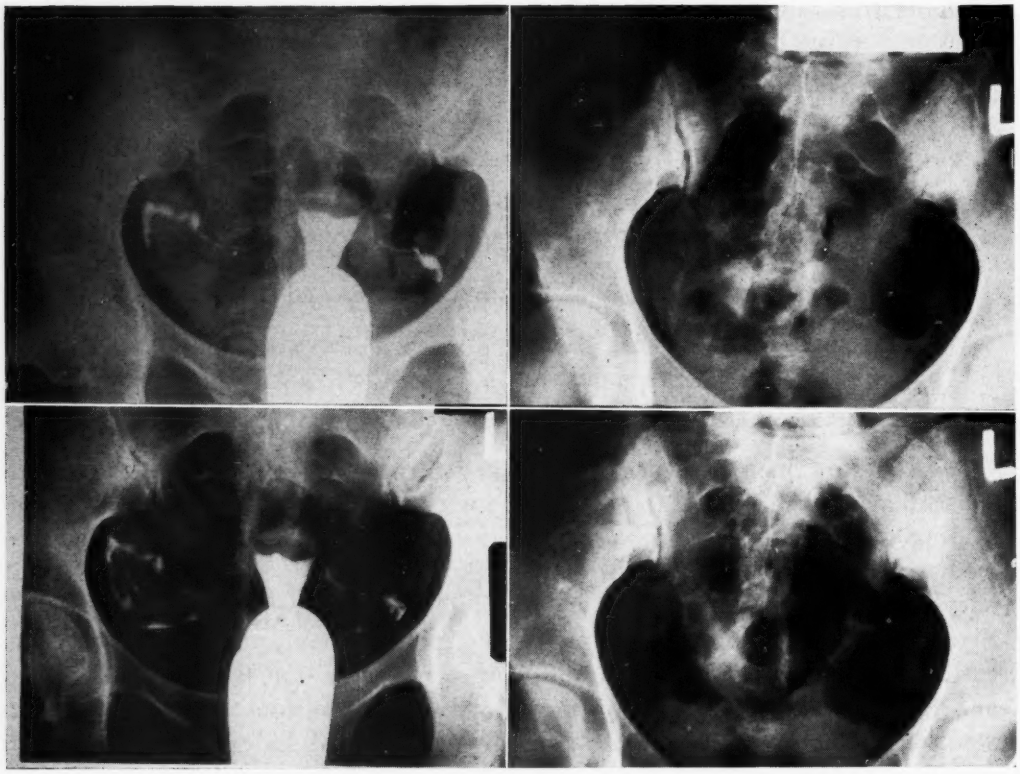

Fig. 1 (Case A. B.).—Absorption of Rayopake.
Upper left, Demonstrates tubal filling.
Lower left, Demonstrates peritoneal spill.
Upper right, Complete absorption (45 minutes).
Lower right, Bladder shadow (60 minutes).

The fractional method of injection without manometric control was employed. A total of 8 to 12 c.c. of medium was generally injected. Most of the patients experienced some pelvic discomfort during the procedure. In some, severe cramping pains like menstrual cramps were noted when the uterine cavity was overdistended by too rapid injection. This was relieved by withdrawing a small amount of the medium. Most patients experienced mild discomfort when the medium flowed into the peritoneal cavity. This varied in intensity with the individual patient but generally disappeared within an hour. In each case an attempt was made to demonstrate tubal filling

*See Tables I and II for manufacturer.

and peritoneal spill, and to follow absorption from the peritoneal cavity by a succession of films. Four to six serial films were usually obtained. When aqueous media were used the absorption time was followed by films taken at ten-minute intervals. Patients injected with oily media were filmed at monthly intervals.

Clinical Data

Absorption.—

Rayopake is very rapidly absorbed from the peritoneal cavity and upper genital tract. In 90 per cent of the 52 cases, absorption was complete in 75 minutes; 13 per cent in less than 25 minutes; 71 per cent in between 25 and 45 minutes, and 8 per cent in 45 to 75 minutes (Table I and Fig. 1). In four women (8 per cent), large smooth pelvic x-ray shadows were still present after two to five hours, and at later operation all showed evidence of hydrosalpinx with complete occlusion of the fimbriated tubal ends (Fig. 6). In the majority of the patients, a distinct bladder shadow appeared withon one hour, indicating the rapidity of renal excretion of the substance.

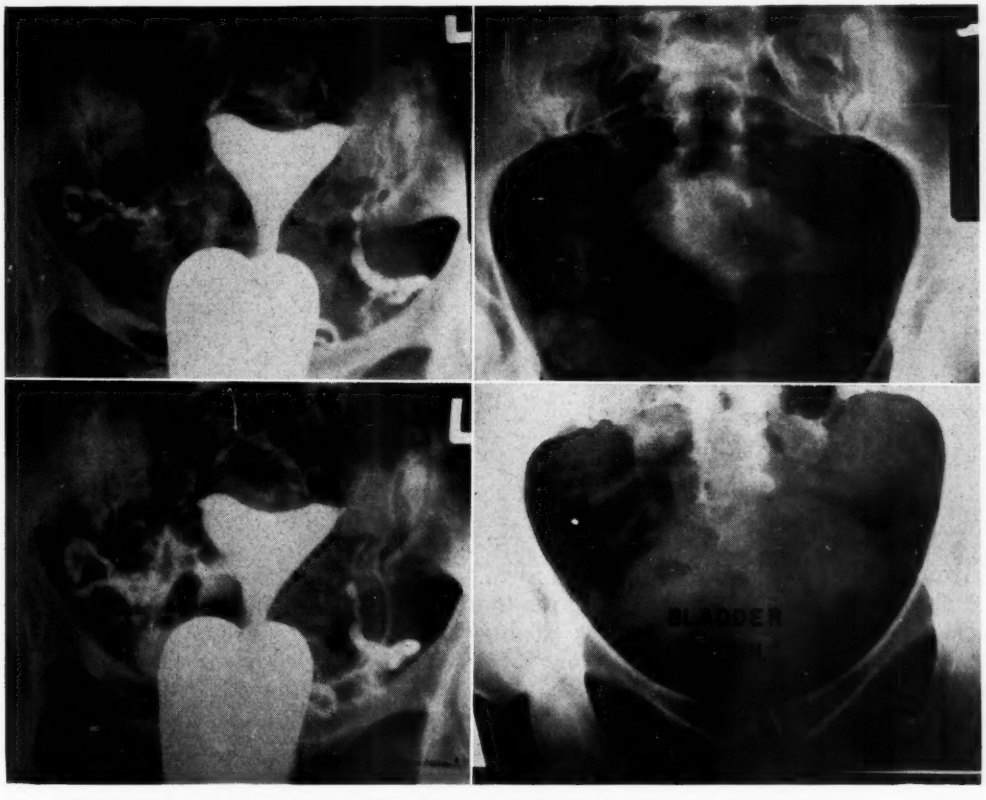

Fig. 2 (Case E. T.).—Absorption of Skiodan acacia.
Upper left, Demonstrates tubal filling.
Lower left, Demonstrates peritoneal spill.
Upper right, Almost complete absorption (25 minutes).
Lower right, Demonstrates bladder shadow (50 minutes).

Skiodan acacia is likewise rapidly absorbed from the pelvis (Table I and Fig. 2). In 84 per cent of the 24 cases, absorption was complete within 75 minutes; 13 per cent in less than 25 minutes; 67 per cent between 25 and 45 minutes; and 4 per cent in 45 to 75 minutes. Four women (16 per cent) showed large smooth x-ray shadows after two to five hours (similar to Fig. 6). Three

of these were found to have hydrosalpinx at operation with complete occlusion of the fimbriated ends of the tubes. Bladder shadows were demonstrated within one hour in the majority, indicating the rapidity of renal excretion of this medium.

TABLE I. ABSORPTION OF AQUEOUS RADIOPAQUE MEDIA

MEDIUM	TOTAL NO. CASES	ABSORPTION TIME							
		LESS THAN 25 MINUTES		25-45 MIN.		45-75 MIN.		2-5 HOURS*	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Rayopake (Hoffmann-La Roche)	52	7	13	37	71	4	8	4	8
Skiodan (Winthrop)	24	3	13	16	67	1	4	4	16

The subjects were injected with 6 to 12 c.c. of the agent and studied by serial films at ten-minute intervals.

*Delayed absorption occurred in eight cases of hydrosalpinx. This is of diagnostic value in determining tubal occlusion.

TABLE II. OILY RADIOPAQUE MEDIA

MEDIUM	TOTAL NO. CASES	PERSISTENCE OF RADIOGRAPHIC SHADOWS*							
		1-3 MONTHS*		3-6 MONTHS*		7-14 MONTHS*		OIL RETENTION CYSTS†	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Lipiodol (Fougera)	16	7	44	5	31	4	25	4	25
Iodochlorol (Searle)	17	11	68	8	32	0		4	25
Lipoidodine (Ciba)	10	5	50	5	50	0		1	10

These subjects were injected with oily radiopaque agents and followed by serial films at monthly intervals. Radiopaque shadows were present when these patients were seen for the last time.

*This represents the length of time these patients were followed; radiopaque pelvic shadows were present when last filmed.

†Thick-walled cystic dilatations of the tubal lumina filled with inspissated oil and bound down in the pelvis by adhesions. Microscopically they show foreign-body reaction, calcification and fibrosis of the tube wall. On x-ray they appear as large isolated pelvic shadows which are quite constant from month to month. They may connect with similar adjacent cystic structures in the pelvis.

Lipiodol is very slowly absorbed from the pelvis. In the sixteen women injected with Lipiodol, x-ray shadows indicating unabsorbed oil deposits persisted throughout the period of observation up to fourteen months; 44 per cent in one to three months; 31 per cent in three to six months; and 25 per cent of the subjects in seven to fourteen months (Table II and Fig. 3). Four of these patients showed fairly large discrete pelvic x-ray shadows which were constant month after month. Two of these women were later subjected to operation and these structures were found to be "oil-retention cysts" (Figs. 3 and 9).

Iodochlorol is also slowly absorbed from the pelvis (Table II and Fig. 4). In sixteen women injected with this medium, the oil shadows were still present one to six months later. Persistent oil shadows were observed in all patients when last seen. Four patients showed persistent x-ray shadows which were constant for six months.

Lipoiodine is also slowly absorbed from the pelvis (Table II and Fig. 5). In ten subjects studied, the absorption time varied from one to six months; fifty per cent of the cases showed persistent oil shadows when last seen at three to six months. One patient presented pelvic x-ray shadows of an oil cyst. It is apparent from a comparison of Figs. 3, 4, and 5 that Lipoiodine is better absorbed than the other oily media. While this series is small (ten subjects) it is our clinical impression that this difference in absorption is significant, and that Lipoiodine is the most rapidly absorbed of the oily agents.

Viscosity and Radiopacity.—

Rayopake: In the 52 patients injected with Rayopake, complete tubal visualization was usually obtained following the first or second serial injection. Subsequent injections demonstrated peritoneal spill and gradual emptying of the tubes. The density of the radiographic shadows was satisfactory in all cases, the details being sharp and distinct (Fig. 1).

Fig. 3 (Case E. F.).—Absorption of Lipiodol.
Upper left, Demonstrates tubal filling.
Lower left, Demonstrates peritoneal spill.
Upper right, Persistence of iodized oil (74 days).
Lower right, Persistence of iodized oil (179 days).

Skiodan: In the 24 patients injected with Skiodan acacia solution, there was such rapid emptying of the tubes after the first or second serial injection that in many instances the peritoneal spill overshadowed the tubal outlines (Fig. 2). For this reason films showing tubal detail were difficult to obtain and not satisfactory. The density of the x-ray shadows, while lightest of the group studied, was satisfactory. The least agitation of this medium produced bubbles which gave false shadows in many films (Fig. 7).

Lipiodol: In sixteen women injected with Lipiodol, there was a more gradual tubal filling permitting excellent tubal visualization. Successive films demonstrated pelvic spill very satisfactorily. The radiographic shadows were excellent, the details being sharp and distinct (Fig. 3).

Iodochlorol: Excellent tubal visualization was obtained in the sixteen patients injected with Iodochlorol. There was gradual emptying of the tubes in each case. Successive films demonstrated tubal outline and pelvic spill very satisfactorily. The radiographic shadows were excellent and the details were sharp and distinct (Fig. 4).

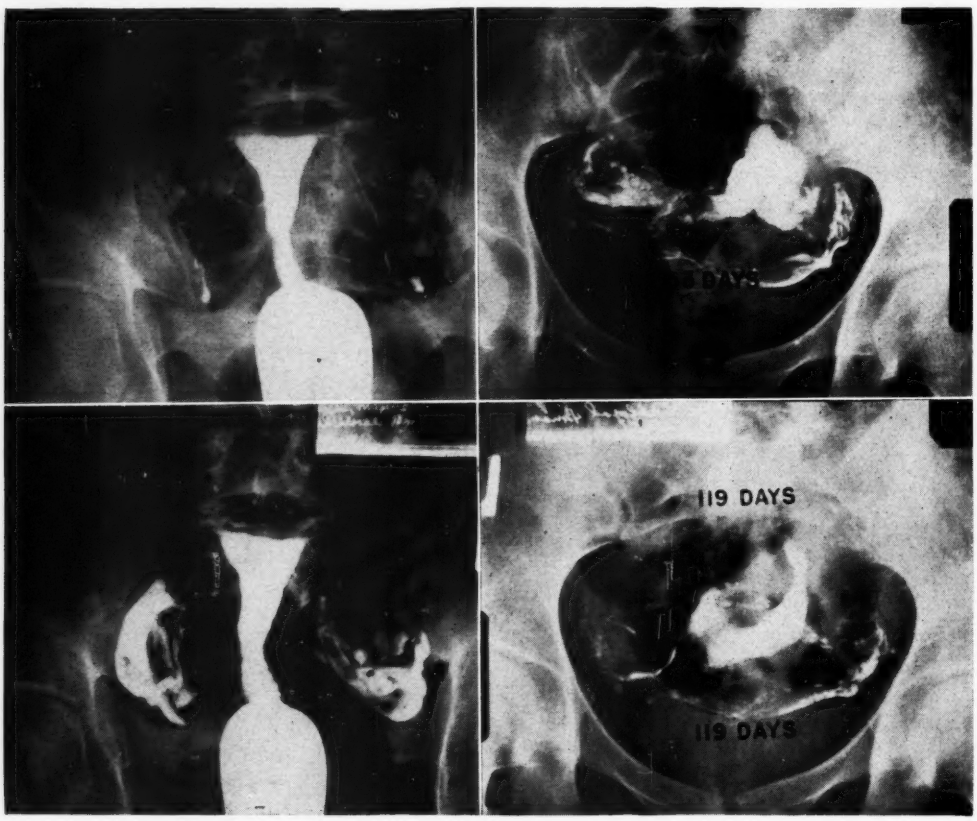

Fig. 4 (Case M. H.).—Absorption of Iodochlorol.
Upper left, Demonstrates tubal filling.
Lower left, Demonstrates peritoneal spill.
Upper right, Persistence of iodized oil (53 days).
Lower right, Persistence of iodized oil (119 days).

Lipoiodine: Ten subjects were injected with Lipoiodine. The low viscosity of this medium permitted too rapid peritoneal spill, which overshadowed the tubal outline and made satisfactory films of tubal detail difficult to obtain. The density of the x-ray shadows was excellent (Fig. 5).

Clinical Reactions.—

Rayopake: One patient (2 per cent) with radiographic evidence of tubal disease developed lower abdominal pain, fever (101° F.), and leucocytosis three days following Rayopake injection. Response to treatment with antibiotics was prompt. Another patient with a history of allergy and drug sensitivity developed generalized urticaria following injection.

Skiodan: Three patients (13 per cent) injected with Skiodan acacia solution developed generalized hives with severe itching; there was no history of allergy or drug sensitivity. They responded to treatment with subcutaneous Adrenalin.

Lipiodol: One of the patients (8 per cent) injected with Lipiodol developed lower abdominal pain, fever (102° F.), and leucocytosis four days following Lipiodol injection. There was no radiographic evidence of tubal disease. Two sterility patients showing isolated pelvic x-ray shadows five and fourteen months subsequent to Lipiodol injection came to operation. These shadows were found to represent occluded tubes in which the iodized oil was entrapped (Fig. 8). These cysts were bound down by adhesions, contained inspissated oil, and the walls showed considerable foreign-body reaction microscopically (Fig. 9). Three other women who had hysterectomies a few days following the Lipiodol injections had from 1½ to 2 ounces of free, brown, serous fluid in the pelvis.

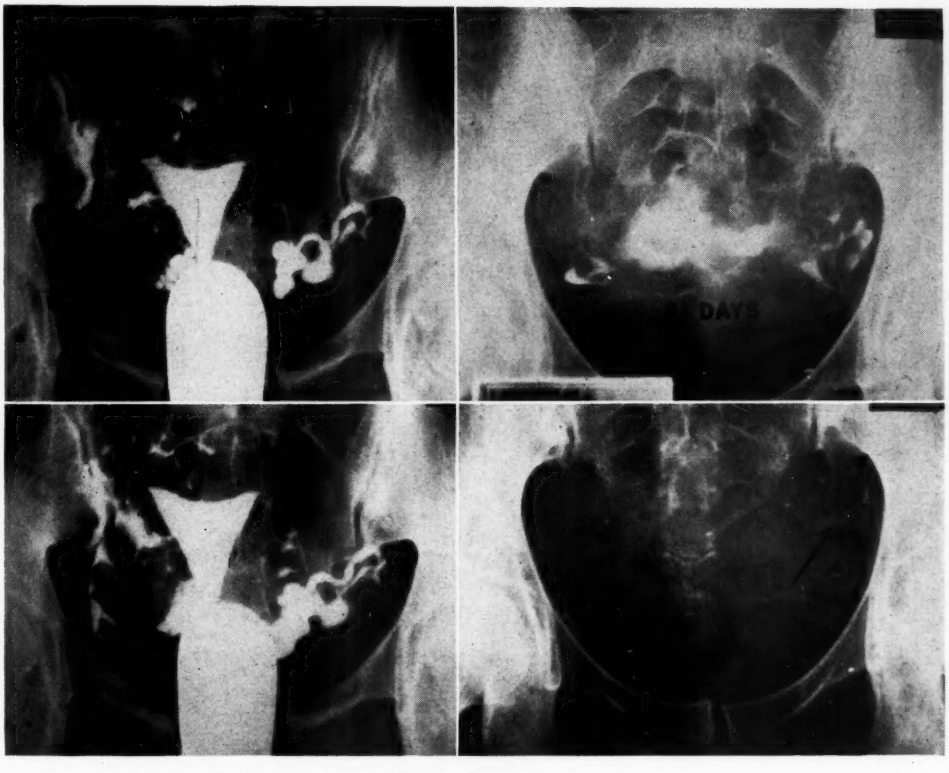

Fig. 5 (Case B. E.).—Absorption of Lipoiodine.
Upper left, Demonstrates tubal filling.
Lower left, Demonstrates peritoneal spill.
Upper right, Persistence of iodized oil (21 days).
Lower right, Persistence of iodized oil (84 days) (almost complete absorption).

Iodochlorol: There were no clinical reactions noted in this group of subjects. At the time of laparotomy following Iodochlorol injection, there were from 1½ to 2 ounces of free, brown, serous fluid in the pelvis.

Lipoiodine: Two cases of severe septic reaction followed the use of Lipoiodine. Although the Lipoiodine series is small and the role of the iodized oil is in doubt, it is of interest that the only woman in this entire series in whom severe septic complications occurred had been injected with Lipoiodine.

Histologic Reactions.—

Tissue reaction to these various media was studied both grossly and microscopically. These observations are being reported separately but may be summarized as follows:

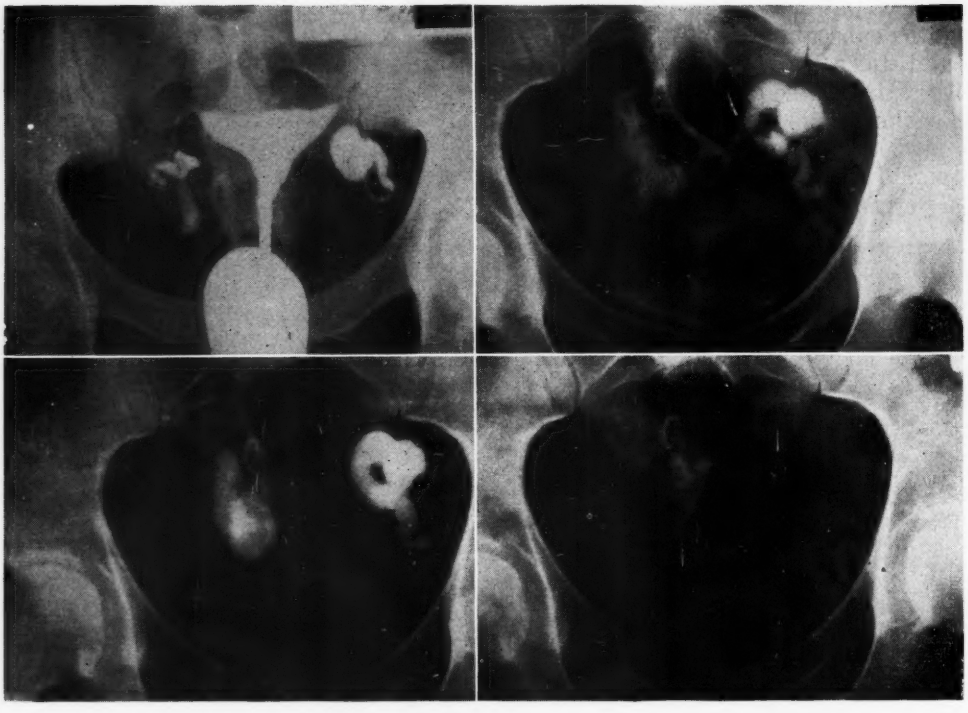

Fig. 6 (Case J. E. C.).—Delayed tubal absorption of Rayopake (hydrosalpinx).
Upper left, Demonstrates tubal filling.
Lower left, Demonstrates tubal shadows at end of one hour.
Upper right, Demonstrates tubal shadows at end of three hours.
Lower right, Demonstrates complete absorption at end of five hours.

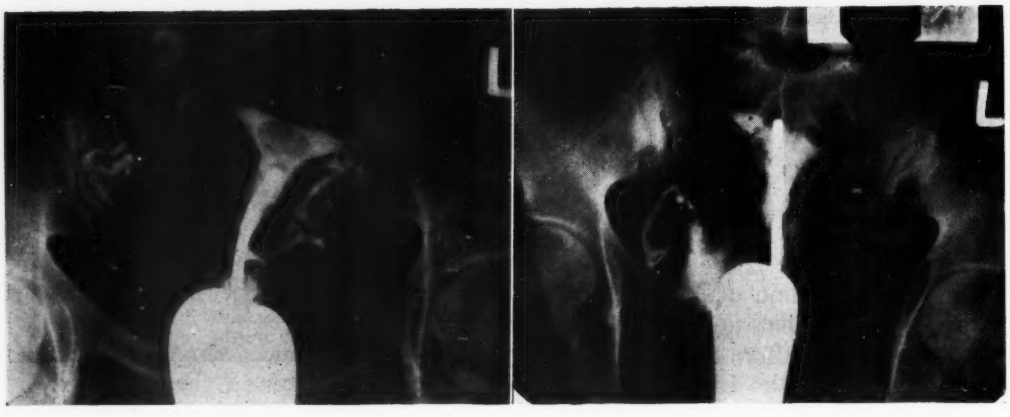

Fig. 7.—Skiodan acacia films showing false intrauterine shadows produced by bubbles.
Right, Many small bubbles.
Left, Large bubble.

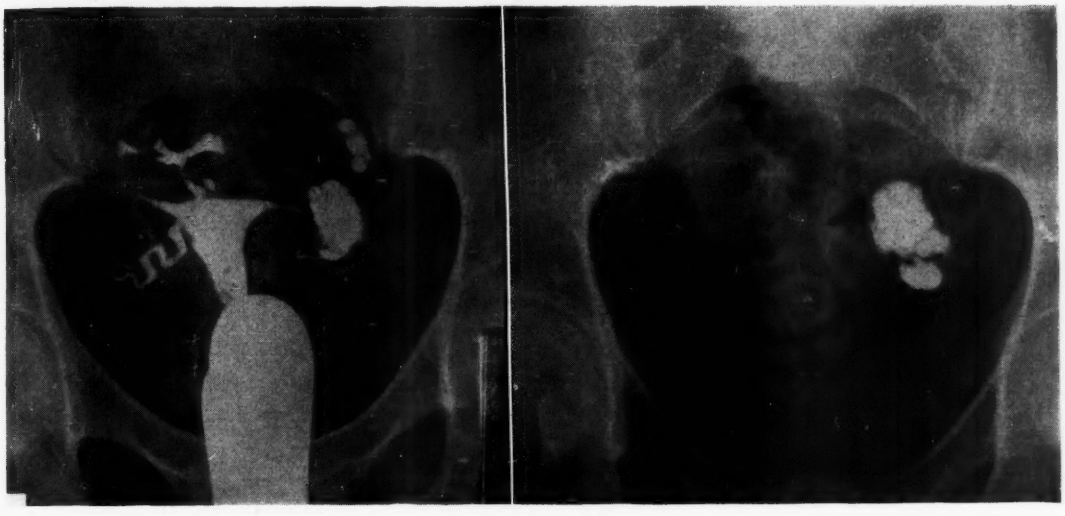

Fig. 8 (Case H. L.).—Lipiodol oil-retention cyst.
Left, Hysterosalpingogram, Sept. 12, 1946.
Right, Left oil-retention cyst, Feb. 12, 1947. (See Fig. 9.)

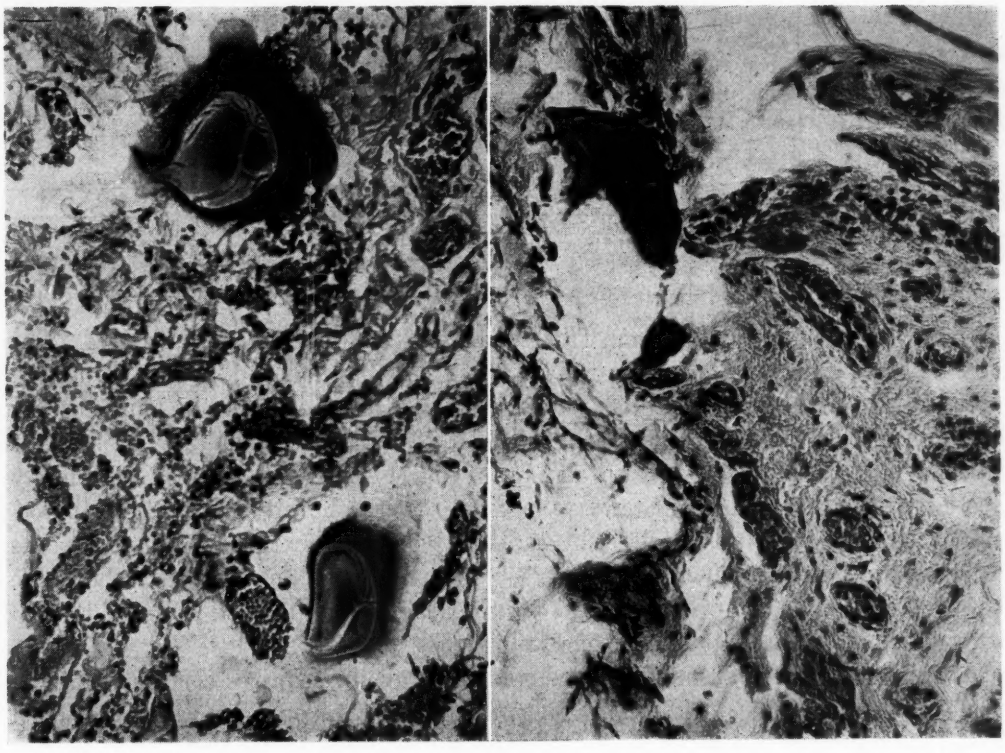

Fig. 9.—Microscopic sections of oil-retention cysts.
Left, Calcification of Lipiodol. Oil-retention cyst found in H. L. (Fig. 8).
Right, Oil-retention cyst showing foreign body giant cells and psammoma body. Iodochlorol, Case G. W.

In normal tubes no significant reaction to either the aqueous media or iodized oils occurs. However, in the presence of partial or complete tubal obstruction, the iodized oils produce foreign-body granulomas which bring about complete occlusion and "oil-retention cysts." Transient acute peritoneal reactions are found in patients injected with the iodized oils. These undesirable effects are not manifested by the aqueous media because of their rapid absorption and nonirritating effects.

Discussion

Clinical results with all the radiopaque substances have been generally satisfactory. While certian individual differences exist, these media can be divided into the oily and aqueous agents and discussed as groups. These observations are tabulated in Table III.

TABLE III. TABULATION OF CLINICAL DATA

	AQUEOUS		OILY		
	RAYOPAQUE 52 CASES	SKIODAN ACACIA 24 CASES	LIPIODOL 16 CASES	IODOCHLOROL 17 CASES	LIPOIODINE 10 CASES
Absorption time	Less than hour	Less than hour	6-9 plus months	6-9 plus months	3-6 months
Route of excretion	Kidney	Kidney	?	?	?
Viscosity	Satisfactory	Unsatisfactory	Requires warming; satisfactory	Requires warming; satisfactory	Solid at room temperature; unsatisfactory
Radiopacity	Good	Good	Excellent	Excellent	Excellent
Time of filming	Immediately	Immediately	Delayed	Delayed	Delayed
Clinical reaction allergic and septic (see text)	Rare, 4%	Allergic reaction in 13%	Occasional, 8%	None in this series	20%
Tissue reaction	None	None	Present	Present	Present
Retention cysts	None	None	Present	Present	None seen
Facility in handling	Satisfactory	Poor	Fair	Satisfactory	Fair

Rapidity of absorption constitutes one of the outstanding differences. The oily agents persist in the pelvis for months. The method of absorption and excretion has not been determined. The aqueous media on the other hand are absorbed within 20 to 40 minutes and are excreted through the kidney; a bladder shadow is usually visible within an hour (Fig. 1). In partially or completely occluded tubes the shadows tend to persist. With the oily media it is impossible to determine with certainty by radiography whether the shadow represents an oil pocket in the peritoneal cavity or trapped oil in an occluded tube. The aqueous media on the other hand show a characteristic delayed absorption pattern which is not present in peritoneal spill (Fig. 6).

This rapidity of absorption of the aqueous group requires certain modifications in radiographic technique. The patient must be on an x-ray table when injected and films taken at once. Physicians who are accustomed to injecting patients in their offices and sending them to the radiologist for films would object to the rapid absorption of the aqueous media. This apparent disadvantage is easily compensated for, and is more than offset by, the many disadvantages associated with the persistence of iodized oil in the pelvis.

The radiographic shadows of both types of agents are satisfactory. Although the aqueous media produce less dense shadows than the oily preparations, this presented no difficulties.

The viscosity of the radiopaque media also plays an important part in the accurate diagnosis of tubal disease. The medium must be sufficiently viscous to remain in the tubes long enough to permit satisfactory x-ray films. Most of the agents studied were satisfactory in this regard. The viscosity of Rayopake and Iodochlorol is satisfactory. Skiodan Acacia on the other hand is considerably less viscous, the material spilling into the peritoneal cavity so rapidly that the tubes are occasionally empty on filming, or the peritoneal spill overshadows the tubal outline.

Lipiodol and Lipoiodine require warming prior to use. This is especially true of Lipoiodine which is solid at room temperature. Heating to liquefication so reduces the viscosity of the oil that unsatisfactory radiographic films similar to those described for Skiodan Acacia are often obtained. It is apparent from these studies that viscosity plays an important part in obtaining satisfactory radiographic shadows. Rayopake of the aqueous and Iodochlorol of the oily group were most satisfactory from this standpoint.

The physical properties of these agents are important from the standpoint of satisfactory handling. The necessity of heating Lipiodol and Lipoiodine is a distinct disadvantage. Skiodan Acacia solution is a sticky substance, frequently causing the plunger of the syringe to bind; it also occasionally forms bubbles on agitation and if accidentally introduced into the uterus or tubes may give false shadows.

Patients experience some discomfort with hysterosalpingography and it frequently is necessary to administer a narcotic. Pain associated with this procedure is of three types: the discomfort associated with attaching the tenaculum and introducing the cannula; the pain of utreine distention; and the pain associated with peritoneal spill. The amount of discomfort experienced by patients in each of these three categories varies widely. Some authors have tended to assign more or less pain to some one of the agents used. This study offered an opportunity to inject a number of patients with two or more media, thus providing an opportunity to compare the several substances in the same patient.

The discomfort of the tenaculum and cannula cannot be significantly altered. The pain associated with uterine distention can be minimized by slow injection of the medium and, if significant, can be relieved by the withdrawal of a small quantity. The discomfort associated with peritoneal spill varies little with the different agents used. The degree of pain seems to reflect the patient's sensitivity to the peritoneal spill of a foreign substance rather than to the chemical characteristic of the agent employed.

The observed clinical reactions predominate with two substances. Thirteen per cent of the patients injected with Skiodan Acacia developed hives. Lipoiodine was associated with severe pelvic infection in two patients; one developed an abscess requiring drainage, and the other a chronic cellulitis requiring sev-

eral months for resolution. While this series is small it is of interest that two of the three febrile reactions and both the septic complications occurred with Lipoiodine.

Tissue reaction to these agents may be immediate or delayed. Both seem to be absent with the aqueous media. Oily substances produce a transient peritoneal reaction as manifested by brownish fluid and edema of the pelvic peritoneum in twenty-four and forty-eight hours, and filmy adhesions in a week. Persistent oil in the pelvis frequently produces oil-retention cysts, chronic granulomas, and psammoma bodies. The earliest time at which this reaction was found was seventy-one days; others ranged from twelve to fourteen months. Patients who apparently have partially occluded tubes may suffer complete closure as a result of this chronic inflammatory change in the tube induced by the persistence of iodized oil.

Summary

1. Hysterosalpingograms were obtained on two hundred subjects in a study of aqueous and oily radiopaque media. The clinical problems encountered with these agents are outlined.

2. Absorption of radiopaque materials varied from 25 to 45 minutes with aqueous media to 3 to 6 months with the iodized oils.

3. Satisfactory radiographic visualization of the upper genital tract was obtained with Rayopake of the aqueous media and Lipiodol and Iodochlorol of the oily media.

4. Iodized oils have the following *advantages:*

   a. Dense radiographic shadows.
   b. Longer period (several hours or days after injection) during which x-ray films for tubal patency can be taken.

5. The oily media have the following *disadvantages:*

   a. Retention of oil for months.
   b. Transient acute peritoneal reaction.
   c. Development of oil retention cysts with foreign-body granulomas and psammoma bodies.
   d. Oil emboli (none observed in this study).

6. Aqueous radiopaque media have the following *advantages:*

   a. Rapid absorption.
   b. Rapid renal excretion.
   c. Satisfactory physical properties for handling.
   d. Elimination of the hazard of "oil-retention cysts" and pulmonary emboli.
   e. Satisfactory radiographic shadows.

7. The aqueous radiopaque media have certain limitations:

   a. Rapidity of absorption, requiring that films be taken within 5 to 10 minutes after injection.
   b. Low viscosity of Skiodan Acacia permitting too rapid peritoneal spill, overshadowing the tubal outlines.

Conclusions

The aqueous radiopaque agents are preferable in hysterosalpingography because of their rapid absorption and relative freedom from the many untoward reactions encountered with the oily media.

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Rouques, L.: A Practical Method to Encourage Suckling in Premature Infants, Presse méd. **56**: 433, June 19, 1948.

The author reviews Laura Landucci's article entitled "The sympathomimetic amines in the treatment of the premature infants" which appears in Il Lattante **18**: 598-602, 1947. She cites Gaal and Katona's study wherein they used the hydrophosphate of alpha-phenyl-Beta-isopropylamine upon 71 cases. They concluded that a dosage of 2.0 mg. administered three times daily provided an efficient means of increasing the amount of breast milk taken by prematures.

Landucci used another derivative of benzedrine, namely Beta-phenyl-isopropylamine upon fourteen prematures—the average weight was around 1,400 Gm. In all cases the quantity of milk consumed by each was rapidly increased with the prematures responding as actively as infants at term to suckling. They cried before feeding and slept soon after. None showed signs of drug intolerance.

She uses 1.0 mg. in a morning dose which if insufficient is gradually increased, little by little, up to 4.0 mg. in two doses. The drug is not used at night so the premature can sleep without stimulation. In general, after eight to twelve days, the prematures were sufficiently developed that the drug could be dropped at the end of these times.

CLAIR E. FOLSOME.

Derobert, L.: Bronchial Obstruction of the Newborn. Intrauterine Suffocation, Presse méd. **56**: 444-445, June 23, 1948.

The author illustrates, with the aid of six illustrations, three black and white microphotographs and three colored drawings, that bronchial obstruction, caused not only by amniotic fluid but also by plugs of vernix caseosa, albumin, mucus, or blood clots, produces severe asphyxia phenomena. These observations justify more serious attempts at removal of such bronchial obstructions. The illustrations are excellent. CLAIR E. FOLSOME.

A FOLLOW-UP STUDY OF TWO HUNDRED FORTY-THREE CASES OF ECLAMPSIA FOR AN AVERAGE OF TWELVE YEARS*

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THE primary purpose of this study is to throw some additional light on the much discussed question of whether or not eclampsia leaves irreparable vascular and renal damage and is a causative factor in subsequent hypertensive cardiovascular disease.

Two hundred forty-three cases of eclampsia in 138 white patients and 105 Negroes, occurring at the University Hospital, Augusta, Ga., from 1919 to 1947, were followed and the patients were seen and studied at least once from one to twenty-eight years later, the average length of time being 12.3 years—13.9 years for the white patients and 8.2 years for the Negroes.

Most of these women were interviewed and examined during the period from Jan. 1, 1948, through Aug. 31, 1948. In some cases when the patients themselves could not be found, the information was taken from hospital records of subsequent admissions, if such charts contained adequate information.

Material

Age.—The mean age at the time of follow-up examination was 32.6 years. The Negro women were about 6 years younger than the white, 29.2 and 35.4 years, respectively.

Subsequent Pregnancies.—During this time there had been 565 subsequent pregnancies in 188 women. Seventy-seven and four-tenths per cent of the women had at least one additional pregnancy. Eighty-three and three-tenths per cent of the white women had 341 pregnancies and 69.5 per cent of the Negro women had 224 pregnancies. The smaller number of pregnancies among the Negroes is due in part, of course, to the shorter average period of time elapsed. It may also be due to the high incidence of gonorrheal salpingitis in these women.

The Fetus.—Of the 565 pregnancies, 436, or 77.2 per cent, resulted in live-born infants and 129, or 22.9 per cent, resulted in either stillbirths or abortions.

No attempt was made to differentiate between stillbirth and abortion because of the inability of many of these women to give an accurate history. Also, the figure given for the fetal mortality should probably be higher, because there are undoubtedly a certain number of abortions not recalled, some early ones not recognized, and perhaps some criminal abortions which were concealed. This, of course, would raise not only the incidence of fetal mortality, but the total number of pregnancies as well.

Taussig[1] has proved that no statistics on abortion are ever entirely accurate, and Greenhill[2] and Stander[3] also bring out this point. However, going on the assumption that one set of figures may contain approximately the same percentage of errors as another, we may make some comparison to the usual incidence

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of stillbirths and abortions. Stander[3] reports an incidence of stillbirths of 2.14 per cent, and from 8 to 10 per cent abortions. Greenhill[2] says that in the United States in 1944, 39.8 labors out of 1,000 did not result in a live infant. This is an incidence of 3.98 per cent stillbirths. It may be seen, therefore, that in these pregnancies there was a fetal mortality almost twice as great as would be expected. Dieckmann,[4] Rucker,[5] Sym,[6] and others have noted a similar increase. This is in line with the "toxemic sequence" of Young[7, 8] but not necessarily due to "some morbid influence" in their bodies as he concluded. This will be discussed later.

Subsequent Toxemia.—At least 203, or 36.1 per cent of all subsequent pregnancies, were complicated by toxemia. Of those women with subsequent pregnancies, 106, or 56.4 per cent, had at least one episode of toxemia. The figures are probably too low, due to the unreliability of the history, as mentioned in regard to abortion, but we may safely say that the incidence of toxemia was at least four to six times greater than would be expected in the general run of pregnancies.[1, 3, 4, 24, 25] Other authors[4-23] have also found an increase in the number of toxemias in posteclamptic and posttoxemic pregnancies, and Page and Cox,[14] from collected statistics, state the the incidence is eight to ten times more than that usually found.

TABLE I. NUMBER OF PATIENTS INCLUDED IN THIS STUDY, MEAN PERIOD OF TIME COVERED, MEAN AGE AT LAST FOLLOW-UP EXAMINATION, AND NUMBER OF PREGNANCIES SUBSEQUENT TO THE ORIGINAL ATTACK OF ECLAMPSIA

	NUMBER OF PATIENTS	MEAN NUMBER OF YEARS FOLLOWED	MEAN AGE AT TIME OF FOLLOW-UP	NUMBER OF SUBSEQUENT PREGNANCIES	NUMBER OF WOMEN WHO HAD SUBSEQUENT PREGNANCIES	PER CENT OF WOMEN WHO HAD SUBSEQUENT PREGNANCIES
White	138	13.9	35.4	341	115	83.3
Negro	105	8.2	29.2	224	73	69.5
Total	243	12.3	32.6	565	188	77.4

TABLE II. FETAL MORTALITY OF SUBSEQUENT PREGNANCIES AND INCIDENCE OF SUBSEQUENT TOXEMIA

	PER CENT OF SUBSEQUENT PREGNANCIES WHICH RESULTED IN STILLBIRTH OR ABORTION	PER CENT OF SUBSEQUENT PREGNANCIES WHICH WERE TOXEMIC	PER CENT OF WOMEN WITH SUBSEQUENT PREGNANCIES WHO HAD SUBSEQUENT TOXEMIA	PER CENT OF SUBSEQUENT PREGNANCIES WHICH WERE ECLAMPTIC	PER CENT OF WOMEN WITH SUBSEQUENT PREGNANCIES WHO HAD SUBSEQUENT ECLAMPSIA
White	23.2	39.3	63.5	5.3	14.8
Negro	21.9	30.8	45.2	4.0	12.3
Total	22.9	36.1	56.4	4.8	13.8

TABLE III. INCIDENCE OF TOXEMIA IN PREGNANCIES OCCURRING PRIOR TO THE ORIGINAL ATTACK OF ECLAMPSIA IN THESE WOMEN

	NO. OF PREGNANCIES PREVIOUS TO THE ORIGINAL ATTACK OF ECLAMPSIA	NO. OF WOMEN WHO HAD PREVIOUS PREGNANCIES	PER CENT OF WOMEN WHO HAD PREVIOUS PREGNANCIES	PER CENT OF PREVIOUS PREGNANCIES WHICH WERE TOXEMIC	PER CENT OF WOMEN WITH PREVIOUS PREGNANCIES WHO HAD PREVIOUS TOXEMIA
White	130	45	32.6	7.7	15.6
Negro	157	37	35.2	7.6	21.6
Total	287	82	33.7	7.7	18.3

Subsequent Eclampsia.—There were eighteen subsequent attacks of eclampsia in seventeen white women and nine attacks in nine Negro women. The incidence of repeated eclampsia was 4.8 per cent. Thirteen and eight-tenths per cent of the women with subsequent pregnancies had eclampsia twice and one had eclampsia three times.

The old idea that eclampsia is never repeated has been disproved many times, but Dieckmann[4] says he has never seen a case, and Stander[3] says it rarely recurs. Peters,[13] however, reports eclampsia seven times in one patient, and six times in another. Greenhill[2] and Dieckmann[4] give the average rate of recurrence as 10 per cent. Page and Cox[14] from collected statistics found an incidence of 10.5 per cent. Other authors[2, 12-17, 19, 26-31] give rates of recurrence varying from 1.7 per cent to 21 per cent.

Stander[3] reports the usual incidence of eclampsia to be 0.15 per cent. Dieckmann[4] says the rate of occurrence in the United States is 0.66 per cent. Therefore the incidence of repeated eclampsia in this series is from seven to thirty-two times as great as in eclampsia in the general population.

Previous Pregnancies.—Previous to the original attack of eclampsia, there had been 287 pregnancies in 82 women. Thirty-two and six-tenths per cent of the white women and 35.2 per cent of the Negroes had had one or more previous pregnancies.

Of these pregnancies, in at least 22, or 7.7 per cent, there was a history of toxemia. The incidence was essentially the same in white and Negro pregnancies, 7.7 per cent and 7.8 per cent, respectively. On the other hand, 15.6 per cent of the white multigravidas and 21.6 per cent of the Negroes had at least one previous episode of toxemia. This is approximately the general incidence of toxemia.[3, 4, 24, 25, 32] These figures, of course, are no more reliable than those on subsequent toxemia; probably less so because of the time elapsed.

Mortality.—Twenty-seven patients died during the period of follow-up. Two white and two Negro women died of eclampsia, an incidence of 14.5 per cent. Two white and three Negroes died of some manifestation of hypertensive cardiovascular disease, 18.5 per cent. One white woman and two Negroes died of chronic glomerulonephritis, or 14.8 per cent of the total mortality. Three cases of pulmonary tuberculosis, one case of postoperative heart failure after a leg amputation in a diabetic, one stab wound, one cancer of the breast, one cancer of the larynx, one case diagnosed as nonspecific diarrhea, one thyrotoxicosis, one pneumonia post partum, one case of asphyxiation, and three cases undiagnosed accounted for the rest of the mortality. There may have been other deaths during this time, but if so they occurred outside of this state.

TABLE IV. DEATHS DURING THE PERIOD OF FOLLOW-UP STUDY

	TOTAL NUMBER OF DEATHS	PER CENT DIED OF ECLAMPSIA	PER CENT DIED OF CARDIO-VASCULAR DISEASE	PER CENT DIED OF CHRONIC GLOMERULO-NEPHRITIS	PER CENT DIED OF OTHER UNRELATED CAUSES
White	11	18.2	18.2	9.1	45.5
Negro	16	12.5	18.75	18.75	50.0
Total	27	14.5	18.5	14.8	47.8

Subsequent Hypertension.—Twenty-two white women and twenty-five Negroes were found to have a blood pressure of 140/90 or more at the time of follow-up examination. Those with either a systolic or a diastolic pressure in this range were included. Five patients with a blood pressure of 140/80 and two whose blood pressure was 140/70 were thereby included. It is quite possible

that they did not have hypertensive cardiovascular disease. Since in many cases only one blood pressure reading was made, probably others are included who should not have been. Three patients known to be hypertensive before their attack of eclampsia were excluded, as were one with thyrotoxicosis, thirteen who were in the last trimester of pregnancy at the time, and six known to have chronic glomerulonephritis or chronic pyelonephritis. The reasons for exclusion of the last group will be discussed below. The incidence of hypertension according to these standards was 21.4 per cent, 17.7 per cent in the white women and 26.0 per cent in the Negroes.

Different investigators have used different standards to determine hypertension, and of course the number of patients and the periods of time elapsed have varied, so comparison to other follow-up studies is difficult. Teel and Reid[9] followed 80 eclamptics 7.6 years. Using a systolic pressure of 150 as a standard, they found an incidence of 27.5 per cent hypertension. However, among those known to have had normal blood pressure previous to the eclampsia, the rate was only 10 per cent. Reid and Teel,[33] studying pre-eclampsia, found hypertension in 51 per cent of cases in which the previous blood pressure was not known. Among those known to have been without previous hypertension, the incidence was 21 per cent after mild pre-eclampsia and 2 per cent after severe. Chesley, Somers, and Vann,[10] in a recent study of 240 eclamptics followed one to eight years, found a subsequent blood pressure of 140/90 or more in 15 per cent. Light recently found 30.1 per cent hypertension in a follow-up of nonconvulsive toxemic patients. Dexter and Weiss[24, 25, 34] say 25 per cent of patients have hypertension after toxemia. Page and Cox[14] report that in 13,000 cases of toxemia collected from the literature, the incidence is 43 per cent. Dieckmann and Brown[4, 16, 31] report an average of 27 per cent subsequent hypertension after eclampsia and 34 per cent after nonconvulsive toxemia from the literature. In their own series they had an incidence of 37 per cent and 40 per cent after eclampsia and pre-eclampsia, respectively. Stander[3] said that from one-fifth to one-tenth have residual vascular damage. Other authors[5, 11, 15, 17, 18, 20, 24, 33-38] give figures varying from 13 per cent to 63.4 per cent.

TABLE V. INCIDENCE OF HYPERTENSION FOUND AT FOLLOW-UP. ALL PATIENTS WITH A SYSTOLIC PRESSURE OF 140 OR MORE, OR A DIASTOLIC PRESSURE OF 90 OR MORE, ARE CLASSIFIED AS HYPERTENSIVES

	PATIENTS WITH B.P. 140/90 OR MORE		PATIENTS WITH B.P. LESS THAN 140/90	
	NO.	PER CENT	NO.	PER CENT
White	22	17.7	116	82.3
Negro	25	26.0	80	26.0
Total	47	21.04	196	21.4

Subsequent Hypertension According to Age.—The average age of the women with hypertension in this series was 39.8 years, 43.7 years for the white patients and 35.2 years for the Negroes. When we break this down into age groups, we find the incidence of hypertension from 20 to 29 years to be 2.4 per cent in the white women and 14.5 per cent in the Negroes. In the 30 to 39 age group we find 16.7 per cent and 31.1 per cent for white and Negro. The percentage from 40 to 49 years was 29.6 and 66.6, respectively. In those over 50 years of age, five white women and one Negro had hypertension, or 62.5 per cent and 50 per cent. The total incidence of hypertension was 8.9 per cent, 22.5 per cent, 41.0 per cent, and 60.0 per cent, respectively, for the four age groups. Of course the number in each group is much too small to be of any statistical value, but the results do show the general trend.

Master, Marks, and Dack,[39] in 6,366 women, mostly white workers in industry, found a blood pressure of 140/90 or more in 39.27 per cent of women

between 40 and 49 years of age. Hypertension is more common in the Negro race. Schultze and Schwab[40] report that it is 2.5 times more frequent in Negroes than in whites, and 1.5 times more frequent in Negro women than in Negro men. Adams[41] says that the average blood pressure is 7 points systolic and 4 points diastolic higher in Negro men than in white men. According to mean age and race, therefore, we find little, if any, increase in hypertension among our patients, judging from the figures above. However, when we divide our cases into age groups, we find a definitely higher percentage of hypertensives among the younger women. There is certainly no increase in the older age groups.

TABLE VI. MEAN AGE OF HYPERTENSIVE GROUP AND INCIDENCE OF HYPERTENSION AT DIFFERENT AGES

	MEAN AGE	PER CENT WITH HYPERTENSION 30-39 YEARS	PER CENT WITH HYPERTENSION 30-39 YEARS	PER CENT WITH HYPERTENSION 40-49 YEARS	PER CENT WITH HYPERTENSION 50 YEARS-ABOVE
White	43.7	2.4	16.7	29.6	62.5
Negro	35.2	14.5	31.1	66.6	50.0
Total	39.8	8.9	22.5	41.0	60.0

Proteinuria.—Six of the women with hypertension, or 12.8 per cent, were found to have at least a trace of albumin in their urine at one examination. In those without hypertension, four patients, or 2.6 per cent, showed proteinuria. These figures are of little real value since about half the examinations were made on voided specimens. However, the incidence among the hypertensives is not high, as many of them were old severe cases with concomitant nephrosclerosis, and certainly the incidence in the nonhypertensives is negligible.

Comparison of Subsequent Pregnancies Among Those With and Without Hypertension.—

There were 106 subsequent pregnancies in 34 women in the hypertensive group and 459 pregnancies in 154 women of those found to have normal blood pressure at follow-up. Seventy-two and three-tenths per cent and 78.6 per cent of women in each group, respectively, had at least one subsequent pregnancy.

Among the women with hypertension there was an incidence of abortion or stillbirth of 17.0 per cent. The incidence in the nonhypertensive group was 24.2 per cent. It is surprising that the fetal mortality should be higher in the latter group, as hypertensive cardiovascular disease in itself, without superimposed toxemia, is supposed to cause a high fetal mortality.[4, 24, 42] Sharkey and Hess,[43] however, also found no increased mortality in their hypertensive patients, and as mentioned previously, these figures must be taken with some reservation.

Thirty-two and one-tenth per cent of these pregnancies were complicated by toxemia in the hypertensive group, as were 36.8 per cent in those with normal blood pressure. Fifty-two and nine-tenths per cent and 57.1 per cent of women in each group, respectively, had at least one toxemic pregnancy. Although this is in line with the above findings, and tends to confirm them, these figures are even more surprising, as hypertension is generally accepted as one of the causative factors in toxemia.[4, 24]

There were four subsequent attacks of eclampsia in four patients among those found to have hypertension, and twenty-two cases in twenty-one women in the group without subsequent hypertension, an incidence of recurrence of 3.8 per cent and 4.8 per cent in the two groups, respectively. These figures, in contrast to those concerning toxemia and abortion, may be presumed to be accurate, as no woman is likely to forget an attack of eclampsia, and, in addition, most of them were hospitalized in this institution. This also tends to confirm the approximate accuracy of the above questionable data.

TABLE VII. COMPARISON OF SUBSEQUENT PREGNANCIES IN THE HYPERTENSIVE AND NONHYPERTENSIVE

	NUMBER OF SUBSEQUENT PREGNANCIES	PER CENT OF WOMEN WHO HAD SUBSEQUENT PREGNANCIES	PER CENT OF SUBSEQUENT PREGNANCIES WHICH RESULTED IN STILLBIRTH OR ABORTION	PER CENT OF SUBSEQUENT PREGNANCIES WHICH WERE TOXEMIC	PER CENT OF WOMEN WITH SUBSEQUENT PREGNANCIES WHO HAD SUBSEQUENT TOXEMIA	PER CENT OF SUBSEQUENT PREGNANCIES WHICH WERE ECLAMPTIC	PER CENT OF WOMEN WITH SUBSEQUENT PREGNANCIES WHO HAD SUBSEQUENT ECLAMPSIA
Hypertensive	106	72.3	17.0	32.1	52.9	3.8	11.8
Nonhypertensive	459	78.6	24.2	36.8	57.1	4.8	13.6

Comparison of Previous Pregnancies.—Previous to the original attack of eclampsia in this study, there were 82 pregnancies in 21 women among the hypertensives, and 205 in 61 women in those with normal blood pressure at follow-up. Of these pregnancies, 7.3 per cent were toxic in the first group and 7.8 per cent in the second. Among those who had previous pregnancies, 19.0 per cent of the women without hypertension and 18.0 per cent of those with subsequent hypertension had at least one pregnancy complicated by toxemia.

TABLE VIII. COMPARISON OF PREGNANCIES OCCURRING PRIOR TO ORIGINAL ATTACK OF ECLAMPSIA IN THE HYPERTENSIVE AND NONHYPERTENSIVE GROUPS

	NUMBER OF PREVIOUS PREGNANCIES	PER CENT OF WOMEN WHO HAD PREVIOUS PREGNANCIES	PER CENT OF PREVIOUS PREGNANCIES WHICH WERE TOXEMIC	PER CENT OF WOMEN WITH PREVIOUS PREGNANCIES WHO HAD PREVIOUS TOXEMIA
Hypertensive	82	61.8	7.3	19.0
Nonhypertensive	205	31.1	7.8	18.0

Summary and Conclusions

In summarizing the above data we describe 243 cases of eclampsia followed for an average of 12.3 years. The mean age was 32.6 years at this time.

There were 565 subsequent pregnancies in 188 women, of which 22.9 per cent resulted in either stillbirth or abortion. This fetal mortality is almost twice as great as that expected in general.

Of these pregnancies, at least 203, in 106 women, were complicated by toxemia, an incidence of 36.1 per cent. Fifty-six and four tenths per cent of the patients have had at least one toxemic pregnancy. This is four to six times the general rate of occurrence.

Eclampsia recurred 27 times. One woman had two subsequent attacks. The incidence of repeated eclampsia was 4.8 per cent, or from seven to thirty-two times greater than the usual rate of occurrence as reported by various authorities.

Previous to the original attack of eclampsia, there were 287 pregnancies in 82 women. Of these, 7.7 per cent were toxemic. This is approximately the usual incidence of toxemia.

Twenty-seven women died during the follow-up period. Four (14.5 per cent) died of eclampsia, five (18.5 per cent) of some manifestation of cardiovascular disease, and four (14.8 per cent) of chronic glomerulonephritis.

Forty-seven, or 21.4 per cent, were found to have a blood pressure of either 140 systolic or more or 90 diastolic or more. The incidence in the white women was 17.7 per cent and in the Negroes 26.0 per cent. Some of these were single readings.

The mean age of those women found to have hypertension was 43.7 years for the white women and 35.2 years for the Negroes. For women in this age group, the incidence is not significantly high. However, among the younger women hypertension was found more frequently than would be generally expected. Eight and nine-tenths per cent of those from 20 to 29 years old had an elevated blood pressure.

The incidence of abortion or stillbirth and of toxemia was found to be lower in the subsequent pregnancies of those found to have hypertension than in those with normal blood pressure. This was also true in those pregnancies preceding the original attack of eclampsia in these women.

Now, what do these data tend to show in regard to the relationship of eclampsia to cardiovascular-renal disease?

As stated above, although it has been said that eclampsia causes chronic nephritis, six patients diagnosed as having chronic glomerulonephritis or chronic pyelonephritis have been omitted in figuring the incidence of hypertension in this series.

Many authors[12, 21, 22, 23, 44, 45] have reported an incidence of chronic nephritis up to 74 per cent in follow-up studies of eclampsia and toxemia. However, Dieckmann[4, 16, 31] and Dexter and Weiss[24, 25, 34] have pointed out that in most cases this diagnosis was made on hypertension and/or proteinuria alone. Although Acosta-Sison[46] reports the pathological lesion of eclampsia as a nephritis, and Peters[13] and Addis[47] state that eclampsia is identical with acute glomerulonephritis, Bell[48] and Herrick and Tillman[11] have proved that the kidney lesions found both in acute eclampsia and in follow-up studies are of a degenerative rather than an inflammatory nature, that is, nephrosclerosis rather than glomerulonephritis. The follow-up studies of Browne and Dodds[20] and Teel and Reid[9, 33] bear this out. Dieckmann[4] and Dexter and Weiss[24] conclude that the preponderance of evidence leaves no doubt that eclampsia is not a nephritis, nor does it cause chronic nephritis.

Therefore, since the only relationship that chronic glomerulonephritis bears to eclampsia is that of a possible contributory causal factor, those cases were excluded. Obviously, chronic pyelonephritis cannot result from eclampsia per se.

But does eclampsia leave behind some residual vascular damage? Does it result in subsequent hypertensive cardiovascular disease?

Dexter and Weiss,[24, 25, 34] who have done a great deal of careful work on the subject in the last few years, are convinced that toxemia often causes irreparable damage. Greenhill,[2] Stander,[3] Gibberd,[23] Harris,[44] Young,[7, 8, 19, 30] Peckham,[12, 38, 45] Peters,[13] Herrick and Tillman,[11] and many others are proponents

of the theory that there are sometimes or always residuals. Teel and Reid[9, 33] conclude that eclampsia causes little damage but that nonconvulsive toxemia perhaps causes more.

On the other side of the argument, Dieckmann[4, 49] and Dieckmann and Brown[16, 31] have probably done more work than anyone else in this country. They are equally convinced that the true toxemias of pregnancy cause no permanent damage. Chesley, Somers, and Vann,[10] Light,[50] McClellan, Strayhorn, and Densen,[35] and Browne and Dodds[20] have all presented follow-up studies which they interpret as confirming this viewpoint. Icenhour, Kuder, and Dill[51] examined 900 nulliparous women and 900 parous women and found no more hypertension in the latter group. Barnes and Browne[52] made a similar study of 915 nulliparous and 1,044 parous women with similar results. Theobald[53] examined the death reports for England and Wales for the years 1911-1920 and found that the incidence of death from arteriosclerosis and Bright's Disease was higher in single than in married women. However, Golden, Dexter, and Weiss[25] cast some doubts on the statistical significance of his figures.

This study indicates that eclampsia does not cause hypertensive cardiovascular disease, although as indicated by the higher incidence found in the younger women, it may aggravate a pre-existing condition, causing it to be clinically evident at an earlier age.

Although only cases of eclampsia were included in this study it is felt that the same conclusions may be drawn in regard to pre-eclamptic toxemia as well. The work of Dexter and Weiss,[24, 25, 34] Peckham,[38] Teel and Reid,[9] Harris,[44] Gibberd,[23] Young,[7, 8] and others is interpreted as indicating that the duration of the toxemia is the important factor in causing permanent vascular damage. They feel that the severity of the attack is of secondary significance. But, on the other hand, although the word eclampsia means "to flash forth," implying a condition of sudden onset, it is well known as Greenhill[2] and Stander[3] have both pointed out, that in most cases convulsions are preceded for some time by the signs and symptoms of toxemia. Although eclampsia may occur occasionally, with apparently no premonitory signs, it is nearly always the end result of a long-standing and neglected toxemia. It seems reasonable, therefore, that if pre-eclampsia leaves residual damage, eclampsia should do so as well, and that if eclampsia causes no permanent vascular changes, then neither should pre-eclampsia.

One reason for the high incidence of subsequent hypertension found in many follow-up studies of nonconvulsive toxemia is, as Dieckmann,[4] Dexter and Weiss,[24, 25, 34] and Teel and Reid[9, 33] have brought out, that many cases diagnosed as mild pre-eclampsia are, in reality, cases of essential hypertension to begin with.

What is the significance of the relative incidence of toxemia in the hypertensive and nonhypertensive groups? Dieckmann[4] believes that true toxemia seldom if ever recurs. He says that those patients who have repeated toxemias are actually cases of essential hypertension. The information gained from this study certainly does not bear out this belief. Of course the finding of a slightly higher incidence of toxemia in those patients with a normal subsequent blood

pressure than in those with hypertension is of little statistical significance, but, on the other hand, these apparently normal women have been followed for an average of 12.3 years. They have had an average of three pregnancies each, of which 36.8 per cent were toxemic. One would expect that if they had had a latent or potential hypertensive cardiovascular disease, it would have become clinically evident by this time.

In conclusion, it may be said that according to the results of this study, eclampsia is a specific disease of pregnant women. It is not a manifestation of chronic nephritis, nor of hypertensive cardiovascular disease, although either of these conditions may precede the attack of eclampsia and possibly render the patient more susceptible to toxemia. Neither does eclampsia nor nonconvulsive toxemia cause chronic nephritis or hypertensive cardiovascular disease. Patients who have once had eclampsia or pre-eclampsia are more likely to have subsequent toxemia and a high incidence of stillbirths and abortions, following the "toxemic sequence" of Young.[7, 8, 19, 30] This is not, however, because of some constitutional weakness "or morbid influence," as he suggested, not because they are essential hypertensives, as Dieckmann[4] states, nor is it because the first attack leaves them more susceptible; but rather, it is because the same etiological factors—environment, diet, etc., are very likely to remain more or less constant and to provoke the same results in subsequent pregnancies.

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Discussion

DR. LESTER WILSON, Charleston, S. C.—Reports of autopsies upon women who have died some years after apparently recovering from eclampsia are few and are concerned chiefly with changes in the kidneys. In one patient who died seven years after having had eclampsia many glomeruli were found to show focal scars which Bell interpreted as having resulted from the eclampsia. Kellar and Baird and Dunn, and others, found no significant changes in kidneys of women, autopsied one or more years after the original eclampsia, who did not have hypertension. Patients with persistent postpregnancy hypertension following eclampsia or pre-eclampsia usually show at autopsy the nephrosclerosis characteristic of hypertensive vascular disease and no lesion characteristic of eclampsia. Bell's interpretation of focal glomerular scarring as a post-eclamptic renal lesion has therefore never been substantiated.

From the clinical viewpoint there is also difference of opinion, as the authors have pointed out. Even with the knowledge of this controversy, I am not fully convinced that eclampsism does not damage the vascular-renal system in normal women without inherent predisposition to hypertensive vascular disease. The authors' report of an unusually high incidence of hypertension in the young groups tends to bear this out. I have some objection to the paper itself in attempting to prove so important a point as this. No prepregnancy hypertension figures are given; the age at onset of hypertension in relation to age at time of pregnancy is not given; and, in some instances, only one blood pressure was taken. In other words, there is no attempt to individualize patients and to show what changes took place in them as individuals. Where this has been done, as Dexter and Weiss have shown, the inference has been drawn that eclampsism does cause vascular-renal damage in more women than would have had such damage had they not developed eclampsism. I heartily agree that eclampsia tends to repeat itself in patients whose environment continues to predispose to eclampsia, but I do not believe that this is the whole story.

Studies of this sort should emphasize to us the importance of careful follow-up on patients who have had pre-eclampsia or eclampsia. The vascular and renal systems should be carefully examined for evidence of postpregnancy hypertensive vascular disease or a predisposition to this disease, before future pregnancies are advised. A careful family history of hypertension is valuable. Repeated blood pressure determinations and urinalyses, including search for casts as well as albumin, specific gravity, and renal function tests should be done. Funduscopic examination will rarely be of value unless there is definite hypertension. The cold pressor test has been used in patients with postpregnancy hyper-

tension to indicate a predisposition to severe hypertensive vascular disease. When such women again become pregnant, environmental and controllable causes of the original eclampsism should be searched for and eliminated.

DR. R. B. NICHOLLS, Norfolk, Va.—We in private practice are faced with the seriousness of eclampsia on too frequent occasions. This paper is a definite contribution to the general knowledge which is accumulating to help us manage more satisfactorily the severest of the toxemias of pregnancy.

One cannot read the vast amount of literature on eclampsia and be unimpressed by the effect that diet, hygiene, and economic factors have on the incidence of eclampsia.

In a recent survey of eclampsia at the Norfolk General Hospital, over an eight-year period extending backward from 1948, it was shown that eclampsia occurred 26 times in 10,390 deliveries, or .025 per cent. One of the interesting points that I found was that nine cases of eclampsia occurred during the war year 1944. The two years on either side of 1944 showed that there were only three cases in 1943 and one case in 1945. One naturally questions the reason for the sudden rise of eclampsia in that single year. It appears that this high incidence in 1944 could be a deficiency in protein in diet as a result of difficulty in obtaining meat due to rationing. It could be partly an emotional effect of the husbands being in the service or over seas, and it could be partly a result of financial and economic inability to supply the proper foods for the diet.

Of these 26 eclamptics during that eight-year period, 20 had prenatal care and 6 had no prenatal care. There were 14 cases in private patients and 12 cases in clinic patients. Three deaths occurred among the 26 patients, of whom two had had no prenatal care. One could hardly arrive at conclusions from such a small group of patients, but apparently the lack of prenatal care has more effect upon the severity and fatality of the eclampsia than on its occurrence.

Evidence is building up to show that eclampsia as such can occur more than once in the same individual in subsequent pregnancies. A patient who has once had eclampsia, particularly if it is with her first baby, is concerned as to whether or not her chances are increased of having another eclamptic pregnancy. It is not always possible to tell the patient whether she may develop eclampsia or not, but there are several things which, if recognized, will help in determining the prognosis for the patient.

First, if the patient is of an older age group, that is, from 30 years on upward, repeat toxemias are more likely to occur.

Second, if the eclampsia occurred during the first pregnancy her chances are less for recurrence of toxemia than if it occurred during subsequent pregnancies. Leon Chelsey at the Margaret Hague Hospital quotes 42 per cent chance of recurrence after the first pregnancy as against 62 per cent chance in subsequent pregnancies.

Third, the duration of the toxemia in days and weeks seems to have importance in the prognosis for future pregnancies. The longer the duration of the toxemia the greater the repeat incidence of toxemia. Quoting Chelsey again, "If the toxemia was for one week or less there is a 20 per cent chance; one to two weeks, 41 per cent chance; two to three weeks, 50 per cent chance; and more than three weeks, 83⅓ per cent chance of repeat toxemia."

Fourth, the more promptly the blood pressure and urine return to normal after delivery in the eclamptic patient the more favorable the outlook for future pregnancies. If the blood pressure and urine are normal by the tenth day she has a 22 per cent chance of recurrence. If either the blood pressure or the urine are normal after the tenth day there is nearly a 60 per cent chance of repeating toxemia, quoting Chelsey.

Fifth, the more heavily built the patient is, the more likely she is to have another toxemia.

DR. JOHN CROSS, Atlanta, Ga.—The question of the incidence of permanent vascular disease following toxemia of pregnancy is a controversial one. There are many groups of statistics, from clinics in all sections of the country, which will confirm either side of the

question. The authors call attention to the wide difference of opinion among other men, each opinion based on statistics that tend to support it. A very critical analysis of all statistical data should be made in order to make the deductions of real value.

In the present series of 243 eclamptics, it would be interesting to know if this condition had developed in women with previously normal cardiovascular renal systems. A table giving the number of eclamptics, and the year each case occurred, would help in the follow-up study of cases. It would be advisable to include the incidence, the severity, and the duration of the pre-eclampsia in these cases. These are important and variable factors which have received a great deal of attention by several writers in their evaluation of posttoxemic vascular and renal complications.

The number of Negro patients and the number of white patients in the hypertensive and nonhypertensive groups is not given. There is enough difference in the incidence of toxemia in the two groups to justify parallel series throughout the study. The combined statistics, covering both white and Negro patients, give data that cannot be compared accurately with any other reports.

A diagnosis of hypertension, often borderline, can be very misleading if it is based upon one blood pressure reading not preceded by a few minutes' rest. The finding of a higher incidence of subsequent toxemia in the nonhypertensive than in the hypertensive group is certainly unusual. Since the term toxemia can be very inclusive, I think that a definition of what is meant by subsequent toxemia would be necessary in analyzing the results. The conclusion that repeat toxemia is the result of some etiological factor such as environment, diet, etc., and not the manifestation of chronic glomerulonephritis or a premature cardiovascular change, cannot be disproved. However, I do not think the statistics as given are sufficiently conclusive to establish environment, diet, etc., as the probable etiologic factors.

It seems that from all the work done during a considerable period of time on the subject of toxemia in pregnancy, there are only a few facts that stand out. These are:

Toxemia manifests itself during the latter half of pregnancy as an acute vascular disorder characterized by a generalized angiospasm causing anoxemia and accompanied by an increase in the permeability of the vessel walls and by hypoxia to some of the tissues, depending on the anatomical distribution of the vascular tree.

These clinical findings and a few years of experience observing a large number of cases of toxemia in pregnancy, mostly in the Negro race, have impressed me with the increased incidence of hypertension and nephrosclerosis following toxemia of pregnancy. The main contributing factors are: first, the duration of the disease; second, the age of the patient; and finally, the severity of the disease.

In closing, I want to thank Drs. Torpin and Bryan for giving us these statistical data on so large a series of eclamptics followed for such a long period of time. It is from such exhaustive studies as theirs that much data will be obtained to aid in determining the incidence and type of posttoxemic vascular and renal complications, if any.

Fernandez-Ruiz, R. M.: The Intrapelvic Injection of Penicillin in Refractive Genital Tract Infections, Toko-ginec. pract. 7: 11-14, Jan., 1948.

The author describes his experiences in the use of intrapelvic injection of penicillin through the cul-de-sac in selected pelvic inflammatory processes, acute and subacute, which had failed to respond to more or less routine chemotherapeutic treatment. He recommends usually an initial injection of 50,000 to 100,000 Oxford Units with repeated dosages totaling 300,000 to 2,000,000 Oxford Units. There is usually a rapid fall of temperature by the third day with early localization and resolution of the inflammatory processes. CLAIR E. FOLSOME.

THE DIFFICULT GENITAL FISTULA; TEMPORARY DESCENSUS UTERI FOR RELIEF OF TENSION*

GEORGE A. WILLIAMS, M.D., ATLANTA, GA.

(From the Department of Obstetrics and Gynecology, Emory University School of Medicine)

IT IS my intention to report the satisfactory use of some of the older and less desirable operations and to present a new method of using an equally ancient principle for the relief of tension on the sutured wound edges.

The basic principles of the management of the genital fistulas are well known and will not be reviewed here. The use of sulfonamides and antibiotics and the new knowledge of physiologic requirements for optimum wound healing have done much to simplify our task but we still have the problem of reducing tension on the wound edges in the large fistulas and in those with extensive scar tissue.

In 1845 Jobert de Lamballe[1] made a transverse incision anterior to the cervix (the "crossbar" of our "inverted T") to free the bladder from the cervix. His pupil, Gustav Simon,[2] used tension-relieving sutures instead of this incision. Sims[3] and Emmett[4] used relaxing incisions combined with massage and dilatation of the vagina with plugs and tampons in preoperative preparation to reduce tension on the suture line.

The anterior surface of the partially prolapsed cervix has been drawn down under the fistula and used to "patch" the defect. The corpus uteri has been interposed and sutured under the defect as in the Watkins' operation by Frank.[5] Kelly[6] in a case of retroversion-flexion brought the corpus out through a cul-de-sac incision and used it for this purpose. In another case he did not hesitate to cut the bladder entirely away from the cervix. No attempt was made to close the resulting defect in the vaginal wall, it being allowed to granulate. Kelly also made extensive use of inverted flaps of the vaginal wall to close fistulas with minimum tension.

We have recently been confronted with the problem of an unusually large vesicourethrovaginal fistula. The entire trigone plus the posterior two-thirds of the urethra were involved (Fig. 1). The ureteral orifices opened on the posterior edge of the fistula. It seems that an operation for cystocele had been performed. A piece of vaginal wall which inadvertently reached the pathologist was reported to be 4 by 5 cm. in size. Troublesome bleeding at the time of operation was controlled by tight packing of the vagina and numerous transfusions. When the pack was removed, the bleeding recurred and the patient was packed again. When this pack was removed, the catheter tip was found in the vagina and complete incontinence ensued. Late massive hemorrhage occurred on the eighth postoperative day and the patient was rehospitalized in shock. She was again packed tightly and when this pack was removed, renewed bleeding led the attendant to attempt closure of the fistula and control of the bleeding by deep blind suturing. This undoubtedly contributed materially to the large size of the fistula.

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

At operation four months later, the tissues were found to be in good condition in spite of widespread scarring of the vagina and adequate mobilization was secured. The bladder and urethral defect could not be approximated longitudinally, so were closed transversely with interrupted sutures of No. 000 chromic gut. The vaginal wall also had to be closed transversely using No. 00 chromic gut interrupted sutures but fortunately the two suture lines were not superimposed. When the cervix was released at the end of the operation, the resulting tension caused two of the vaginal wall sutures to cut through. It appeared that a radical deep incision completely cutting the bladder away from the cervix would be necessary to reduce this tension. Rather than do this, the cervix was brought down to the introitus again and sutured there. A loop of large nylon was passed transversely through the cervix, then through the deep fascia over the ischiopubic rami and tied over the fourchette. The result was quite gratifying and prompt primary union occurred. Because of the discomfort to the patient who required frequent small doses of morphine for backache, the cervical anchoring suture was cut on the eighth postoperative day. Tension again developed but so slowly that although the vaginal wound edges separated slightly, granulation was sufficiently rapid to fill in the defect and good epithelization eventually occurred.

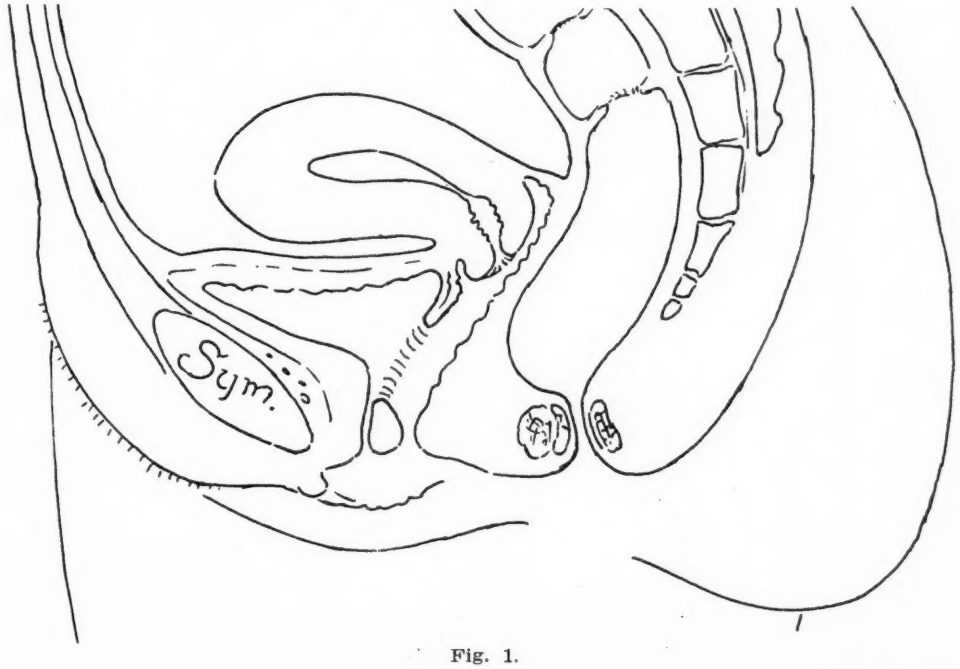

Fig. 1.

There was of course no urethral control and an Aldridge-Te Linde modification of the Stoeckel-Goebell-Frangenheim operation was performed three months later. The left external oblique fascial strip was rather flimsy but a badly scarred old midline incision prevented use of an anterior rectus strip. The result was excellent at first but stress incontinence developed. Six months later operation for removal of a large endometrial cyst of the ovary became necessary and at this time the left half of the Aldridge sling could not be identified. It apparently had completely atrophied. Again using the procedure of Te Linde, a strip of fascia lata was used successfully to replace the atrophied Aldridge loop (Fig. 3).

In consideration of the rather prompt recurrence of the tension on the vaginal suture line which followed release of the temporarily prolapsed cervix, I would not again use a single anchoring stitch but would use sutures on both

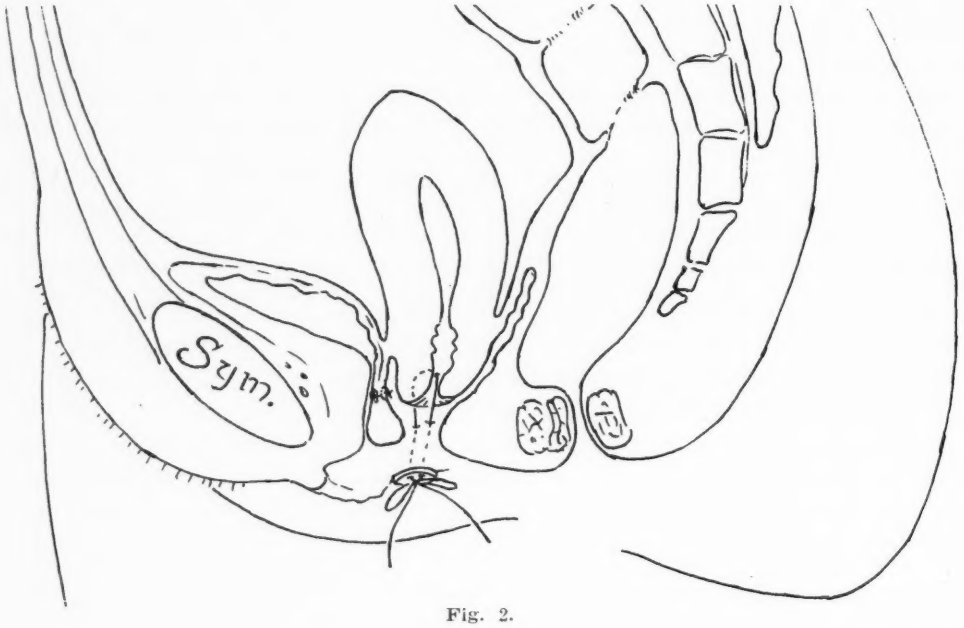

Fig. 2.

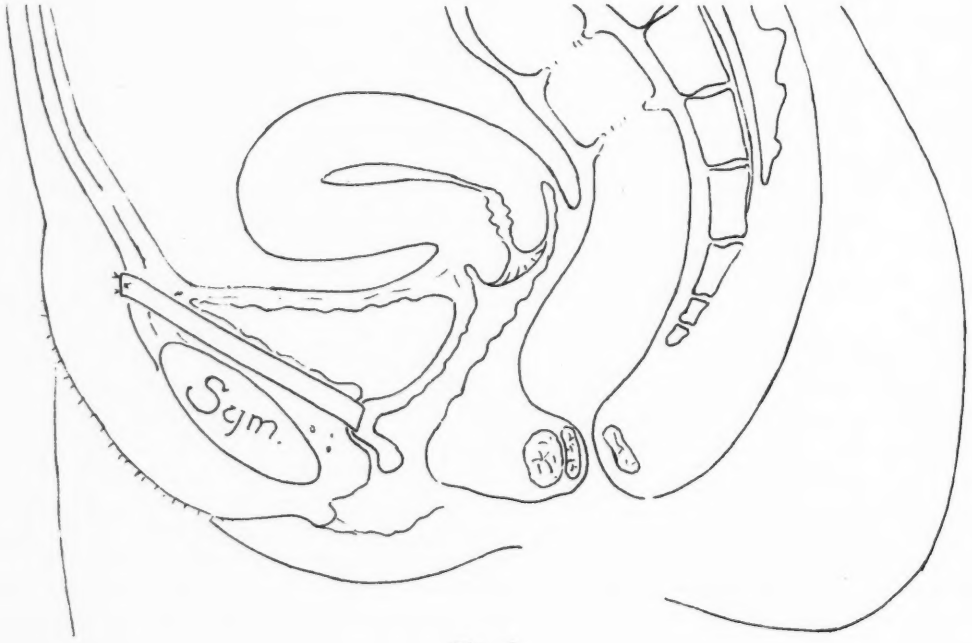

Fig. 3.

sides of the cervix passing through the fascia over the ischiopubic rami and tied over buttons in such a way that the sutures would be gradually lengthened and thus avoid possible disruption of the healing wound (Fig. 2).

Formerly, obstetric injuries furnished the greater portion of genital fistulas and surgery contributed largely through repeated operative failures to the difficulty of eventual management. At the present time better obstetrics results in fewer cases and these in turn have access to good surgery for their repair. In our own experience the most common causes of fistulas are radium-treated carcinoma of the cervix and the loss of tissue due to lymphopathia venereum. One of our most hopeless cases had both etiologic factors.

Management of the two groups differs widely. The tissues remaining after the lymphopathic process is arrested do not lend themselves well to surgery. They are friable, inelastic, and ischemic and the most satisfactory remedy for incontinence is diversion of the urine by transplantation of the ureters to the sigmoid if the disease has not damaged the rectum and/or anus too much.

A determined effort should be made to evaluate the status of the malignancy before any surgery is decided upon for if fistula in a cancer patient is due to malignant disease, the case of course is hopeless. There is, however, not an inconsiderable number of women whose cancer is apparently under control but who have fistulas which make them miserable. Perhaps most of the patients with such cases come to us after heavy radiation of Stage 2 carcinoma with extension to the vagina because it is axiomatic with us that nothing is worse than cancer even though genital fistula may rank a close second in the patient's estimation. It is only fair to confess that an occasional fistula presents itself in our clinic even though the technical problem in the use of radium does not explain it.

The vesicovaginal and rectovaginal fistulas in the radium-treated patient present a different problem from those resulting from obstetric and surgical injury. There is associated with the defect changes in the adjacent tissue: cicatrization, ischemia through radiation effect on blood vessels, fixation of the cervix and uterus through fibrosis, and not infrequently lower ureteral obstruction from periureteral fibrosis with resulting ureterectasis. This emphasizes the need for complete urologic study in all cases to differentiate ureteral blockade due to fibrosis from that due to extension of carcinoma to the ureter. This is best done by repeated dilatation, the latter not responding to such treatment while the former may do so. Many patients with irradiated carcinoma of the cervix have ureterectasis which does not lend itself well to transplantation, however, so attempt at relief from below should be made. In discussion of the management of this group of patients I will draw freely on the combined experience of Dr. John F. Denton and Dr. Calvin B. Stewart and myself at the Steiner Cancer Clinic.

We are frequently able to close a small fistula due to radiation with the usual methods, especially if estrogens are used locally for about ten days in an effort to vascularize the mucosa. We do not think this short course is contraindicated in spite of the theoretical danger of estrogen therapy in cancer patients. Often, however, we find that it is impossible to mobilize the tissues with any of the usual methods of counterincision, etc. For such fistulas high in the vagina Latzko's[7] method may be used. It consists of excision of a cuff of vaginal mucosa about the fistula and suturing the anterior and posterior walls together. Obviously this cannot be done in the presence of a cervix or uterus which requires drainage but may be performed occasionally where the cervix and uterus, if present, have been virtually obliterated through irradiation. It is usually compatible with an active sex life but the other procedures to be discussed are not.

Large vesicovaginal or vesicorectovaginal fistulas may be treated by partial vaginectomy if the sphincters are intact (Figs. 4 and 5). This was first done by Simon[2] in 1848. We have not found it necessary to divert the fecal stream in such cases. These women seem to get along fairly well with a bladder that is in part lined with vaginal mucosa and the ones who have combined fistulas do

not seem to have much ill effect from the presence of feces in the bladder or urine in the rectum. Perhaps these women have suffered so greatly that they complain little of petty annoyances.

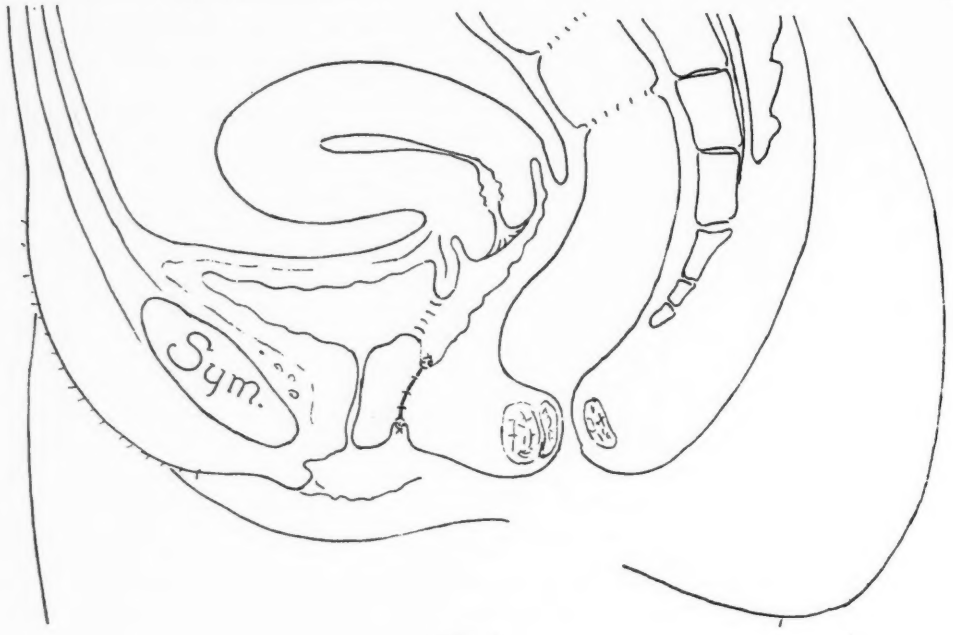

Fig. 4.

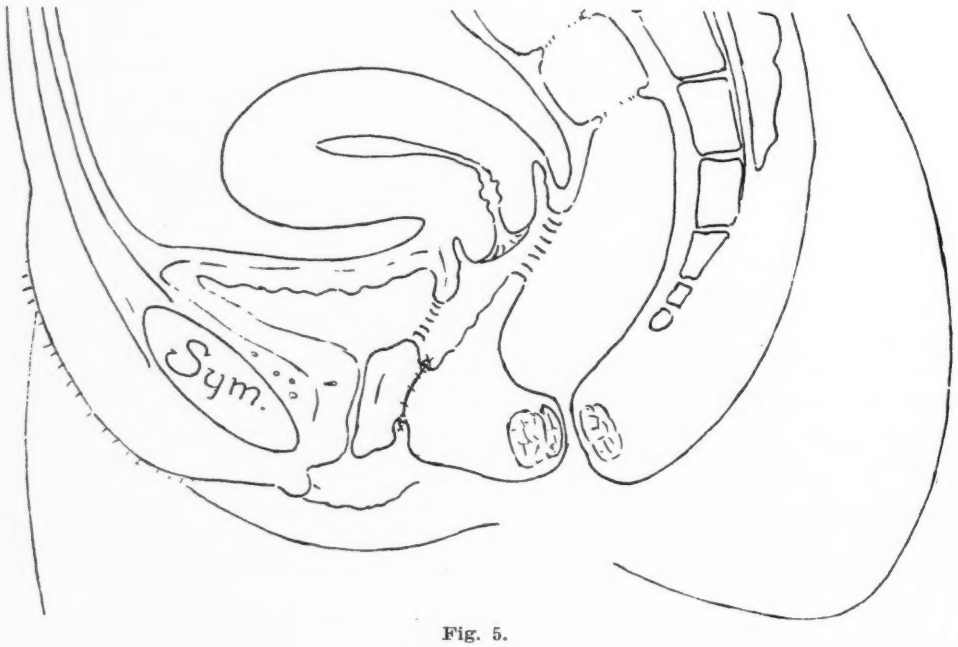

Fig. 5.

Occasionally vaginectomy may be applied to patients with extremely large fistulas. A patient with a Grade 1, Stage 2 carcinoma (extension to the upper vagina) was treated with 7,000 r. of x-ray and 8,000 mc. hr. of radium with

prompt regression but localized recurrence in the cervix and vagina eighteen months later. In spite of the heavy irradiation and the ischemic appearance of the tissues, it was apparent that surgery offered her only chance for salvage. She was apprised of the danger of fistula formation and accepted it. Radical hysterectomy and salpingo-oophorectomy with the removal of the upper third of the vagina was done. When examined seven days postoperatively preliminary to contemplated excision of the vagina from below, the upper half of the remaining two-thirds of the vagina was seen to be undergoing necrosis. Widespread sloughing occurred ten days later. Ninety days later the slough had completed and the ureteral orifices were seen on the posterior edge of the fistula. The remaining third of the vagina was removed. The bladder capacity rapidly improved and the patient is symptom free and shows no evidence of disease eighteen months postoperatively. Although only 47 years of age, she and her husband have accepted the situation philosophically as the only alternative to an otherwise hopeless state (Fig. 4).

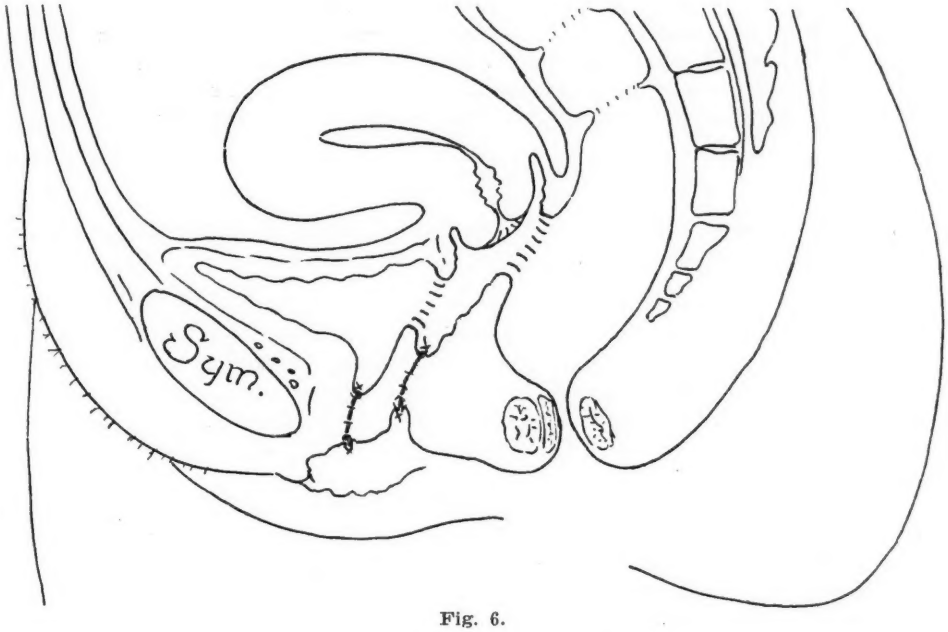

Fig. 6.

One patient whose vesicorectovaginal fistula was treated by vaginectomy was found to have a complete urethral incontinence after the operation. She had stress incontinence previous to her cancer therapy and the worsening was partly due to the resulting genital atrophy and perhaps in part to the vaginectomy being carried too low so that the urethra was pulled open thereby. She was treated by excision of the lower portion of the urethra and closure of the raw surfaces. A small sinus resulted which soon closed spontaneously, all urine being voided per rectum (Fig. 6).

Not all patients are so fortunate. Loss of the trigone along with cicatrization and retraction markedly alters the relationship of the ureteral orifices and angulates the ureter and this makes dilatation quite difficult and sometimes impossible. A patient with a large fistula of the entire trigone was treated successfully with vaginectomy and did well for seven months when it was found that both of the ureteral orifices were again badly obstructed and azotemia was present. The function of the right kidney was completely gone and marked hydronephrosis and hydroureter were present on the left. Attempted dilatation of the stricture from above, i.e., through pelvic ureterotomy, failed of permanence and the patient spent her remaining days with a cutaneous ureterostomy.

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Discussion

DR. WAVERLY R. PAYNE, Newport News, Va.—Dr. Williams has presented this subject in a most comprehensive manner, and I found many points of interest. I fully agree with the principles set forth, and would like to emphasize the importance of considering all such cases as joint problems of the gynecologist and the urologist. The avoidance of tension on the suture line, both of the bladder and the vagina, is absolutely essential to success. The idea of producing a temporary descensus in certain cases seems logical, and I would like to ask if he has considered an external perineal band, such as a metal catheter holder, for attachment of the traction sutures. It is my impression that some extensive fistulas, especially those encroaching upon the ureters, can better be repaired by the intravesical approach from above. The crux of this problem is the individualization of cases from the standpoint of etiology, location, and complicating conditions.

Pascual, Garcia Romeu Y Rivas: The Value and Interpretation of the Rh Factor in Obstetrics in Cuba, Rev. cubana de obstet. y ginec. 9: 123-131, Dec., 1947.

The authors classify the major blood groupings and Rh factor determinations in pregnancy and in different racial mixtures. Among 475 patients of the white race they found 220 (46.3 per cent) group O; 199 (41.8 per cent) group A; 44 (9.0 per cent) group B; and 12 cases (2.9 per cent) of group AB. Among 291 cases of mestizo women (hybrids of white and American Indian blood) were 135 cases (46.4 per cent) of group O cases; 105 (36.0 per cent) group A cases; 44 (15.1 per cent) group B; and 7 cases (2.5 per cent) group AB.

Among 307 women of the Negro race were 153 (49.8 per cent) group O blood; 72 cases (23.4 per cent) group A; 68 cases (22.2 per cent) of group B; and 14 cases (4.6 per cent) of group AB. One hundred males of the yellow race showed 42 instances (42.0 per cent) of group O; 30 cases (30 per cent) group A; 26 cases (26 per cent) group B; and 2 cases (2 per cent) of group AB.

The Rh factor was determined in 1,184 cases distributed as follows by race: (1) white race with 424 cases (87 per cent) Rh positive and 63 cases (13 per cent) Rh negative; (2) mestizos (hybrid white and American Indian) 266 (92 per cent) were Rh positive and only 8 per cent (23 cases) were Rh negative; (3) among 306 of the Negro race, 95 per cent (281) were Rh positive and 5 per cent (15 cases) were Rh negative; while (4) 100 per cent of the 102 Chinese were Rh positive.

Because of these racial variations the authors stress the importance of Rh and major blood group determinations in obstetrical practice in Cuba. CLAIR E. FOLSOME.

THE USE OF PYRIDOXINE AND SUPRARENAL CORTEX COMBINED IN THE TREATMENT OF THE NAUSEA AND VOMITING OF PREGNANCY*

CHARLES W. DORSEY, M.D., ROANOKE, VA.

WITH the exception of abortion, probably nothing which occurs in the first trimester of pregnancy causes more general discomfort to the patient, nor more worry and effort on the part of the obstetrician in his endeavor to correct it, than nausea and vomiting. We are all fully aware of the marked improvement which has been made in the treatment of this condition in the relatively recent years, especially in the true pernicious vomiting, yet certainly, if the experience of others is similar to that of the writer, the control of the milder cases—from a mere uncomfortable morning nausea up to a moderate degree of vomiting—still leaves much to be desired.

It is needless to go into a review of the many varied and some even bizarre treatments now in usage, which approach the problem from practically as many angles as there are measures employed, and with as many variations. Suffice it to say that nearly everything imaginable has been attempted, from therapy based on pure superstition at one end of the treatment scale up to those measures which have as nearly a true physiological background as is possible in any condition where the exact etiological factor is still unknown. As evidence of the multiplicity of drugs employed, it is of interest to note that the Physicians Desk Reference for 1949[1] lists, under the heading of "Nausea—Pregnancy," some twenty-three preparations available through varied drug houses, and its list of such houses and preparations is not complete.

It is the purpose of this paper to present simply and briefly the results obtained with the use of pyridoxine and suprarenal cortex combined in the treatment of sixty-two cases of nausea and/or vomiting of pregnancy, without any attempt whatever to establish a comparative evaluation with other methods. Neither is this looked upon as a panacea, which the author feels will probably never be reached until an approach can be made based on the knowledge of the exact etiology, but merely as another weapon in our armamentarium, which seems to have some advantages over, and fewer disadvantages than, some of the other therapy now in vogue.

Before outlining the method of administration, it might be worth while to refresh our memories briefly on the pharmacological properties and physiological actions of the drugs concerned. Vitamin B_6, or pyridoxine is, according to Goodman and Gilman,[2] ". . . one of the components of the vitamin B complex known to be essential in animal nutrition. Although a discrete vitamin B_6 defi-

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

ciency has not been described in man, evidence has been obtained from the treatment of multiple deficiency states that some of the symptoms accompanying the ingestion of inadequate diets may be the result of a B_6 deficiency. . . . It is a pyridine derivative. . . . There is evidence that the physiological function of vitamin B_6 is linked with the utilization of unsaturated fatty acids. From a pharmacological point of view, pyridoxine is rather inert. . . . In man, intramuscular injections cause pain, but the oral or intravenous administration of 100 to 200 mgm. is without untoward effect. . . .''

The same authorities, Goodman and Gilman,[2] say the following about the adrenal cortical hormones:

''The chemistry of the active principle of the adrenal cortex resembles that of the sex hormones in several ways. There are numerous chemically related compounds, possibly a score or more, obtainable from the cortical tissue, most of which possess some degree of physiological activity, just as there are chemically related estrogens and androgens. There is a marked similarity in the chemical structure of the adrenal cortical and sex hormones, especially the androgens. Also, the esterification of adrenal cortical hormones increases their potency and duration of action. . . . The close relationship of the cortical hormones to testosterone is evident.''

The physiological activities of these hormones are not listed per se, but the authors approach this subject from the angle of the effects of hypofunction or ablation of the gland, and state three such effects: ''(1) A marked abnormality in the metabolism of sodium, resulting in a negative balance of this ion, a fall in the total electrolyte content of the extracellular fluid and a resulting shift in the distribution of body fluids. (2) There is an abrupt increase in the concentration of potassium in the extracellular fluids associated with a decreased renal excretion of this ion. (3) Carbohydrate metabolism is seriously altered as is evidenced by a diminished concentration of glucose in the blood and a greatly reduced glycogen content of liver and muscle.'' They state that all these ill effects can be corrected by the injection of the hormones concerned.

From these facts the rationale and physiological basis of the treatment can be established. If, as is stated above, the ingestion of inadequate diets may be the result of a vitamin B_6 deficiency, then it seems logical to presume that, in the presence of vomiting, an oversupply of this same vitamin might reasonably be effective in changing the metabolic picture so that food could be taken and retained. In like manner, the addition of the adrenal cortical hormones may, as its greatest part in this particular condition, aid materially in correcting the upset carbohydrate metabolism by restoring the proper glucose concentration in the blood. It may also, from its close chemical similarity to the sex hormones, play some part in correcting any abnormal reaction which may have occurred in them.

It should be mentioned that in addition to the exact therapy, such generally accepted supportive measures as bed rest, mild sedation when tolerated orally, repeated small feedings alternating liquids and solids, etc., were used in all cases. Nor were the injections used when the above measures produced the desired results.

The treatment consisted of the intramuscular injection of 25 mg. of pyridoxine combined with 0.5 c.c. of suprarenal cortex (Armour) or adrenal cortex extract (Upjohn). The patient was given two injections at an approximate twenty-four hour interval, regardless of the response to the first injection. Further injections were given as required, the patient being instructed to return at the first reappearance of nausea, and not to delay until vomiting occurred. If there was no improvement following the first two administrations, experience proved that further similar treatments were, in most cases, unsuccessful, and

in those cases hospitalization and the use of intravenous glucose and saline gave prompt relief. This will be discussed further in the consideration of the cases listed as failures.

It may be asked why a second dosage was given to those patients who showed favorable reaction to, and cessation of symptoms from the initial injection. One injection only was given at the time the treatment was first used, but in the great majority of those so treated, symptoms returned to some degree within three to five days. Because of this, the two-treatment routine was adopted, and the results have since been much more favorable, showing a much higher percentage of cures with fewer total injections.

As mentioned above, the series consisted of 62 patients; 30 primiparas and 32 multiparas. Of the primiparas, nine were treated by the one-injection method. Of these, three obtained complete relief, five were cured following a second injection, and one required a third treatment, five days after the second had been given.

The remaining 21 primiparas received the two-injection method, with complete cure in eleven, and improvement in all the others, two of whom had such slight morning nausea remaining that they felt it unnecessary to receive further treatment, one of whom aborted, three of whom had a third, and four a fourth injection before complete cessation of symptoms. Those who received more than two treatments got the third three to five days after the second, and in all cases where a fourth injection was given, it was five days after the third. With a few exceptions. the number of injections needed was in direct ratio to the severity of the symptoms when the treatment was first started.

Thus it will be seen that, in the primiparas, cure was obtained in all cases save that of the one patient who aborted, and she was greatly improved following her second injection. It is likewise apparent that cure was accomplished by one injection in one-third of the cases so treated, three of nine, and in roughly half of those given the two-injection treatment, eleven of twenty-one, with only the initial treatment.

In the case of the multiparas, the picture was somewhat, but not tremendously different. There were twelve treated by the one-injection method with three cures; one required two, three had three, three received four, one needed five, and one had to have ten injections to obtain complete relief. Of the remaining twenty cases treated by the two-injection method, ten obtained complete relief with the two initial treatments, four required three, one received four, on had five, and one needed nine injections before being cured. There were three failures.

So it will be seen, as in the case of the primiparas, that the percentage of cures with one injection was lower than with the initial two-injection routine. There is a moderate variation between the primiparas and multiparas cured by one injection, 33 per cent in the former and 25 per cent in the latter, but the cures with two injections are almost exactly the same, eleven of twenty-one, and ten of twenty. Also, there was definite improvement in all cases except those listed as failures. In both the one- and two-injection series, there was one cure in which more than five injections were necessary.

Let us consider these two patients who needed ten and nine treatments, respectively, before complete relief was obtained. The first was extremely nervous, had been treated for nervous breakdown approximately eighteen months prior to this pregnancy, and had been advised not to attempt any more pregnancies, and told she would probably go crazy if she did become pregnant again. The other eventually was delivered by cesarean section because of premature separation of the placenta at about seven and one-half months' gestation, and at operation a bicornuate uterus was found, with the pregnancy in the small cornu.

The failures were as follows:

1. A gravida iii who had an associated true ptyalism of pregnancy.

2. A gravida ii whose first baby was ten years of age, and who, meanwhile, had two major abdominal operations, one being an oophorectomy because of cystic ovary, and who was treated for acute cholecystitis six months prior to her pregnancy.

3. A gravida v who was an habitual aborter and who aborted spontaneously in her fourth month.

These patients, as previously mentioned, all responded to glucose therapy, the first two eventually delivering normal babies at term.

It would therefore seem that this method of treatment has been successful in all cases uncomplicated by either systemic or other obstetric abnormalities, and, likewise, save in such cases, the cure has been obtained with a maximum of five administrations of the combined drugs.

One tends to recall most vividly those things which are most tragic or dramatic. Since the failures have been considered, may I briefly outline the case in which the most dramatic favorable result was obtained.

The patient was a primipara, aged 20 years, who was approximately eight weeks pregnant when first seen. She had been vomiting severely for two weeks, had lost 14 pounds, and was in such weakened condition that she had to be practically carried into the office. She was given the initial injection, and, because she lived at a distance of sixty miles, was advised to remain at a local hotel overnight, and to return the following day. She did not return, and it was presumed she had returned to her family physician at home. However, twelve days later she reappeared and was not recognized. She felt fine, had gained back twelve pounds of her previously lost weight, and had had complete relief of symptoms with in twelve hours after the injection was given. She had no later difficulties.

The results of the one- and two-injection series are shown graphically in Tables I and II, respectively, and of the total series in Table III.

TABLE I. ONE-INJECTION METHOD, 21 CASES

	PRIMIPARAS	MULTIPARAS
Cured, 1 injection	3	3
Cured, 2 injections	5	1
Cured, 3 injections	1	3
Cured, 4 injections	0	3
Cured, 5 injections	0	1
Cured, more than 5 injections	0	1
Failures	0	0
Total	9	12

TABLE II. TWO-INJECTION METHOD, 41 CASES

	PRIMIPARAS	MULTIPARAS
Improved, took only 2 injections	3	0
Cured, 2 injections	11	10
Cured, 3 injections	3	4
Cured, 4 injections	4	1
Cured, 5 injections	0	1
Cured, more than 5 injections	0	1
Failures	0	3
Total	21	20

TABLE III. TOTAL CASES, 62

	PRIMIPARAS	MULTIPARAS	TOTAL
Cured	27	29	56
Improved	3	0	3
Failures	0	3	3
Total	30	32	62

Summary

1. A series of 62 cases of nausea and/or vomiting of pregnancy treated by the use of pyridoxine and suprarenal cortex combined is presented.

2. The chemistry and physiology of the drugs are briefly reviewed.

3. There were 56 complete cures, with such marked improvement in two and possibly three others that they may also be reasonably considered as cures, making a total of 58 or 59, with a percentage cure of 93.5 per cent or 95.1 per cent.

4. In all cases uncomplicated by coexisting systemic disease or other complication of pregnancy, cure was obtained with not more than five injections.

5. The most effective method of administration is apparently to give two injections at a twenty-four hour interval, these being supplemented by further treatment if and when symptoms reappear.

Conclusion

From the ease of administration, lack of discomfort to and beneficial effects obtained by the patient, it is felt that the injection of pyridoxine and suprarenal cortex combined is a worthy addition to the measures employed in the treatment of the nausea and/or vomiting of pregnancy.

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Discussion

DR. JOHN B. DUNCAN, Atlanta, Ga.—I think from my own experience that patients who really want their babies, in about 98 per cent of the cases, are most cooperative. I can recall only two cases in my practice where it was necessary to do an abortion on account of continued vomiting. These two cases were before vitamin B_6 and adrenal cortex were used, although both patients were admitted to the hospital and given Sodium Amytal and intravenous glucose, with a small daily enema, routine rest in bed, several small meals, and a mild sedative. In spite of all this I had to do a therapeutic abortion. One patient, I might add, had a large cystic ovary on the right side which I removed later on and, subsequently, she became pregnant and I delivered a baby without any trouble.

As Dr. Dorsey has stated, if there is any pathology in the pelvis, it is much more difficult to control the vomiting. For the past several years, I have used vitamin B_6 every other day, in a great many cases, usually for five or six doses, and have had excellent results from about 65 to 75 per cent of the cases, but I am very happy to know that there is another drug available which increases the efficiency and makes the early months so much more pleasant for the patients who are suffering from this extreme nausea.

DR. JOHN BURWELL, Greensboro, N. C.—In the October, 1948, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Dr. M. H. Bertling showed the very high correlation of nausea and vomiting of pregnancy with dysmenorrhea. Sixty-eight and one-half

per cent of those having nausea and vomiting had had dysmenorrhea previously. In his conclusion he stated, "A review of the number of cases obtained in each group in comparison with the number that would be expected on a chance basis alone leads one to the conclusion that there is some common factor between dysmenorrhea and nausea and vomiting of pregnancy that could very well be psychogenic, since there is no obvious common anatomic nor physiologic relationship known."

For years, the Smiths have been working on the endocrinology of menstruation and ovulation. More recently they have found a high fetal salvage using stilbestrol in pregnant diabetics, and in the November, 1948, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, O. Watkins Smith told of the use of diethylstilbestrol in the prevention and treatment of complications of pregnancy in 632 cases. Her cases were observed for threatened abortion, the complications of late pregnancy, and premature delivery. She concluded, "Considering the past obstetric histories of these patients, the course and outcome on stilbestrol gave good indication that the administration of this drug as a preventive measure may be expected to reduce the incidence of those complications of later pregnancy associated with a premature deficiency of the placental steroid hormones, estrogen and progesterone."

My associate, Dr. Bertling, revised his thinking on the psychic aspects of dysmenorrhea and nausea and vomiting of pregnancy and we decided that if nausea and vomiting of pregnancy are a toxemia of early pregnancy it might well be due to a deficiency of the placental steroid hormones, since in most instances it "spontaneously" clears up around the fourth or fifth month, the time the placenta is taking over almost the entire production of the steroids. Thus stilbestrol should be the treatment and we now have been using it since October, 1948, in nausea and vomiting. This deficiency of placental steroid hormones may probably be the exact etiology Dr. Dorsey says has not been found. In our stilbestrol series, we used no supportive measure, but stilbestrol alone.

DR. C. J. COLLINS, Orlando, Fla.—I know of no other condition in which it is more difficult to evaluate the value of a specific treatment than in the nausea and vomiting of pregnancy. We are all aware of the tremendous psychic effect of any treatment in this disorder and this factor is difficult to eliminate when we attempt to arrive at accurate and logical conclusions. I was supplied with pyridoxene for experimental purposes when it was first introduced and tried it on a series of cases with no startling results. I concluded that it was of no more value than thiamine chloride and subsequently administered both of them in 50 mg. doses with, as I thought, better results. I also used adrenal cortex some years ago, giving it often in 1 c.c. doses before each meal. I was not impressed with its value and gave it up. Dr. Dorsey's results with their combined use has certainly been better than I ever obtained from either one alone. This suggests that there may be some synergistic action between them. He has offered a physiologic basis for their use and it appears that in this respect a better case can be made for adrenal cortex. His doses have been small and it is a little difficult to understand how two administrations could correct a disturbed metabolic state sufficiently to cure the patient. However, his results have been so good, one-third of all cases cured with one injection and one-half with two injections, with a total cure of 95 per cent, that his presentation cannot be brushed aside as just another treatment, but must be considered seriously as a scientific approach to a most troublesome condition. He has had three failures in sixty-two cases or about one in twenty. I doubt that many of us have ever found it necessary to hospitalize more patients than that for treatment no matter what his favorite routine may be. The main advantage of his treatment seems to be its prompt beneficial effect and that is what the patient wants, prompt relief. Until our understanding of the etiology of the nausea and vomiting of pregnancy has increased to the point that we can develop a specific treatment, it is our duty to employ that one which offers the greatest promise of relief.

CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS*

Experience in 841 Cases in Private Practice

ALBERT J. KELLEY, M.D., SAVANNAH, GA.

THIS report is somewhat unique in that it covers a rather large series of cases, in all of which one man acted as both anesthetist and obstetrician. From February, 1944, to October, 1948, there were 841 vaginal deliveries under continuous caudal analgesia in the author's private practice. Savannah has no hospital connected with a medical school and there are no well-organized resident and intern staffs. Outside anesthetists are not always available when needed and under these conditions the obstetrician must rely on himself for a satisfactory method of pain relief. Many of the members of this society practice under similar conditions and hence this report should be of interest.

In the past few years there has been a notable increase in the use of various methods to control pain in childbirth. Less and less do we hear that women are "supposed to feel their pains," that "the pains of childbirth are soon forgotten," or that "suffering in childbirth increases a mother's love for her child."

Also during the past few years there has been a decided decrease in the maternal death rate. Due to improved methods, better education of the patient and physician, and due to improved measures of combating infection, the most notable decrease has been in deaths from eclampsia and from infection. Consequently recent reports have shown that bleeding has become relatively more important as a cause of maternal deaths.

Parker and Allison[5] in a report read before this society last year have shown that in Greenville, S. C., hemorrhage accounted for six out of thirty-six deaths in 6,413 deliveries from 1938 to 1942. From 1943 to 1947, hemorrhage accounted for eight out of twenty-seven deaths in 13,676 deliveries.

Several reports[1, 2, 3, 4] have indicated that bleeding is definitely less in cases where some form of nerve block is used as the anesthetic agent. This is logical because any properly administered nerve block does not interfere in any way with normal uterine contractions. Any sedative or general anesthetic must, however slightly, decrease the tone of the uterine muscle and the force of the contractions.

In 841 vaginal deliveries conducted under continuous caudal analgesia there was an average blood loss of 109.5 c.c. This compares very closely with the experience of Vaux and Mitchell[1] in 1,000 cases and with the study of twenty-eight months' experience at Philadelphia Lying-In Hospital as reported by statisticians Collins, Phillips, and Oliver.[4]

Table I shows that 68 per cent of the patients had a blood loss of less than 100 c.c., while only 17, or 2 per cent, had blood loss of over 300 c.c. In this series there was no patient with a blood loss of more than 500 c.c. and only 2 cases reached this figure. This distribution is comparable to the figures of Vaux and Mitchell and, as their review of the literature showed, is far less than in most other published series.

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

TABLE I. BLOOD LOSS IN CUBIC CENTIMETERS

BLOOD LOSS IN C.C.	NO. CASES	PER CENT
0.99	572	68.0
100-199	205	24.4
200-299	47	5.6
300 or more	17	2.0
Total	841	100.0

I have no accurate records as to the amount of bleeding in cases before I adopted the use of caudal analgesia, but in common with all observers I have been imprssed with the greatly decreased bleeding as compared with that when other methods of anesthesia were used.

In all cases all blood was collected in the sterile placenta basin during the third stage. The patients were also observed carefully for one hour after the third stage and any additional bleeding estimated. I have been particularly impressed with the tone of the uterine muscle after the end of the third stage. Very few patients required any massage to maintain a firm hard fundus.

It has been argued that, since placenta previa has been considered a contraindication for the use of caudal or spinal analgesia, necessarily a group of cases with excessive bleeding are excluded from such a report as this. This is, perhaps, a just criticism. However, Thorp[6] used this method in twelve cases of marginal placenta previa with a blood loss of less than 125 c.c. in every case.

I have had several cases in which a marginal implantation of the placenta was not diagnosed until after caudal analgesia had been administered and labor was in progress. In none of these was there excessive bleeding. It is reasonable to suppose that there may have been other cases of low or marginal implantation in which the true condition was not recognized. In common with other observers I have noticed that the uterine tone is increased to the point that Pituitrin should not be used at the end of the second stage. I had previously used 1 c.c. of Pitocin or Pituitrin but soon noted that with caudal there is a danger of a trapped placenta with this routine. As a result, the procedure has been changed to omit any oxytocic until after the end of the third stage. It is immediately apparent, after seeing only a few cases, that uterine tone is better and the bleeding markedly less than most of us have been accustomed to seeing.

What of pain relief? This is the primary reason for using caudal analgesia. Here again my figures rather closely approximate those of others. The results were classed as good, fair, and failure. In the first group there was complete relief of pain. In the second group the greater portion of pain was abolished but the patient had variable amount of pain such as slight pain in either groin or moderate pain at the peak of contraction. In those classed as failures there was little or no relief of pain. As shown in Table II, 759, or 90.2 per cent of cases, had complete relief, 59, or 7 per cent, were classed as fair, and there were 23 failures, 2.8 per cent of all cases.

TABLE II. RELIEF OF PAIN IN CONTINUOUS CAUDAL ANESTHETIC

	NO. CASES	PER CENT
Complete relief	759	90.2
Partial relief	59	7.0
Failures	23	2.8

It should also be noted that my experience more or less parallels that of Ellis and Sheffrey.[3] During the first 100 cases the failures were more common.

With increasing experience in the method, the results have improved. This is partly due to better technical skill in properly placing the needle, better selection of cases, eliminating those cases where it is impossible properly to palpate the sacral hiatus. Also with experience one is enabled to judge better the hysterical or psychologically unstable individuals. These patients, even though relieved of pain, find many other complaints such as nausea. They complain bitterly of numbness of the legs and are totally uncooperative. They are doubtless better off if they are asleep during delivery. Several such individuals had to be classed as only fair in judging results in this series.

Having pointed out that in continuous caudal we have a method highly successful in the relief of the pain of labor and one which definitely is accompanied by less bleeding, it is only fair to note some of the dangers and disadvantages.

Technically, caudal is perhaps more difficult than other forms of anesthesia. It is a technique, however, that can easily be learned by any obstetrician in a comparatively short time. Therefore the objection of technical difficulty is only a relative one.

The patient must be watched in a somewhat different manner than other patients. Because the method is not in widespread use the average student nurse is not trained to watch these patients. The average supervisor of the delivery room has not been trained and hence is distrustful of the method. But it is relatively easy to train any competent obstetrical nurse to care properly for these patients.

It has been argued that caudal analgesia necessitates the more frequent use of forceps. I list this as a disadvantage because most of us were taught the traditional abhorrence of forceps. However, more and more obstetricians in recent years have advocated episiotomy and forceps on all primiparas as soon as the head reaches the perineum. I personally believe that one or two hours of second stage pains accompanied by tremendous voluntary exertion by the mother is prone to produce maternal exhaustion, excessive perineal damage, and increased frequency of cranial injuries.

Table III shows the type of delivery of 848 infants delivered to 841 mothers in this series. Forceps were used in 87.6 per cent of primiparas and 44.1 per cent of multiparas.

TABLE III. TYPE OF DELIVERY IN 848 BIRTHS TO 841 MOTHERS

	PRIMIPARAS		MULTIPARAS	
TYPE OF DELIVERY	NO.	PER CENT	NO.	PER CENT
Spontaneous cephalic	44	9.8	212	52.6
Forceps	389	87.6	178	44.2
Spontaneous breech	1	0.2	11	2.7
Breech extraction	11*	2.4	2	0.5
Total	445	100.0	403	100.0

*Forceps were used on the aftercoming head in only one case.

It is of interest that in twenty-five breech deliveries, it was necessary in only one case to use forceps on the aftercoming head. This attests to the fact that with the perineum well anesthetized and relaxed, delivery of the aftercoming head is relatively rapid and easy.

Much criticism has been levelled at caudal analgesia because of its potential dangers. Some of the criticism has been just and some unjust. Caudal does have its hazards just as does any method of anesthesia or analgesia. It is not within the scope of this paper to dwell on this aspect. I will, however, state that most of the untoward results in caudal analgesia have occurred as a result of ignoring the proper safeguards and precautions as originally set forth by Hingson.[8]

In a report last year[7] I cited two cases of shock produced by caudal in cesarean sections. In these cases the difficulty was undoubtedly due to too rapid and too forceful injection of the drug.

The present report includes only cases of vaginal delivery. In this series there have been no cases of shock, no serious drop in blood pressure, and no serious sequelae. There have been three cases of a mild infection at the site of injection. None of these were serious but in one patient, a diabetic, there was a rather widespread low-grade cellulitis, which did not clear completely for two months.

Some mention should be made also of saddle-block or controlled-level spinal anesthesia. Although I have not included them in this report I have used this technique a good many times, particularly in the past year.

The results with this method are very comparable to those with caudal analgesia. There is good pain relief, bleeding is decreased, and the patient is in good condition afterward. Also, as in caudal, it is very striking to note the lack of narcotization of the babies.

Technically, saddle-block analgesia is easier to give. Hesseltine[9] states that at Chicago Lying-in Hospital they prefer it to caudal because all medical students know how to do a spinal tap; therefore, as interns and residents, they require less teaching to give a spinal anesthetic than is the case with caudal.

One must, however, remember that with saddle-block the entire dose must be estimated in advance. It varies with the height and weight of the patient. In continuous caudal the dose is given fractionally and is therefore easier to estimate accurately.

Duration of saddle-block anesthesia varies from one to three hours. I personally do not like the idea of repeated spinal punctures during a labor. This would seem denitely to increase the hazard of infection but those more experienced than I report no difficulty. Saddle-block anesthesia gives effective pain relief in two to three minutes whereas in caudal from ten to twenty minutes are required to establish complete relief.

I have, therefore, recently used saddle-block in those cases where pains are frequent and tumultuous and where it is apparent that labor will be completed within sixty to ninety minutes. Also, I find saddle-block anesthesia invaluable in cases where the sacral hiatus is not palpable or where caudal is failing to give complete relief of pain.

Aside from these factors I find little to choose between the two methods. I would like to add one word of caution. Do not be fooled by the apparently easier technique of saddle-block. There is many a patient who has been prodded in the back for fifteen to twenty minutes in an attempt to find spinal fluid and in whom the insertion of a needle into the sacrum would be simplicity itself.

Conclusions

1. Eight hundred forty-one cases of vaginal delivery under continuous caudal analgesia have been eminently satisfactory with administration of analgesia and delivery done by one person.

2. In confirmation of reports by other authors, bleeding is found to be minimized, averaging 109.5 c.c. per patient.

3. Pain was completely relieved in 90.2 per cent and partially relieved in 7 per cent of cases.

4. Forceps were used in 87.6 per cent of primiparas and 44.2 per cent of multiparas.

5. A brief comparison is made between caudal and saddle-block analgesia.

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Discussion

DR. W. C. WINN, Richmond, Va.—At the Medical College of Virginia Hospital, caudal analgesia has been used with very gratifying results in patients with toxemia, cardiac disease, and in other cases where it was preferable to avoid inhalation anesthesia.

To administer caudal anesthesia safely and successfully, it should be used only in well-equipped hospitals, and administered by specially trained and competent individuals. The careful selection of patients for its use is extremely important.

When there is a definite indication or need for its use, it is most helpful and a valuable addition to our armamentarium. The obstetrician who has a large practice or heavy teaching responsibilities, however, is not able to remain with the patient constantly during labor. Employing a physician anesthetist for the average uncomplicated labor and delivery would be an additional financial burden for the patient. For these reasons, in my opinion, its use in the average normal labor and delivery is not very practical.

Fried, Paul H.: The Two Hour Pregnancy Test, Based on Rat Ovary Hyperemia, West. J. Surg., page 552, Oct., 1948.

Hyperemia of the rat ovary occurs shortly after the animal is injected with chorionic gonadotropin. The reaction may occur within 10 minutes and is maximum at six hours. This lends itself to a quick, inexpensive test for pregnancy, the accuracy of which may be better than 95 per cent. The two-hour rat test was performed on 516 urine specimens and the reaction compared to that of the Friedman test performed on the same specimens. There were sixteen errors in pregnant and nonpregnant cases for an accuracy of 96.8 per cent. In 200 cases of normal intrauterine pregnancies there were eleven errors for an accuracy of 94.5 per cent. In 100 cases of disturbed pregnancies such as ectopic pregnancy, threatened, and incomplete abortions, where a rapid and accurate test for pregnancy is of the greatest importance, the two-hour test gave a percentage accuracy comparable to the Friedman test. The percentage of error in both was sufficiently high to make dubious the clinical value of either. The greatest incidence of error in the two-hour rat test as compared with the Friedman test is the false negatives.

The technique is described in some detail and is relatively simple. The chief difficulty is found in the comparison of the color changes secondary to hyperemia with the standard color charts. Absence of a sharp, positive endpoint makes necessary considerable experience with the test before accuracy of interpretation is obtained. William Bickers.

CONTINUOUS SPINAL ANESTHESIA IN THE TREATMENT OF SEVERE PRE-ECLAMPSIA AND ECLAMPSIA*

A Preliminary Report of a Study of 24 Cases

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(From The Medical College of Virginia Hospitals)

PRIOR to 1947 the treatment of patients with severe toxemias of pregnancy in The Medical College of Virginia Hospitals had remained about the same for fifteen years. This treatment was outlined in the *Southern Medical Journal* in 1937[1] by one of the authors and again by the same author in the *Virginia Medical Monthly* in 1939.[2]

During the year 1947 in The Medical College of Virginia Hospitals several cases of severe pre-eclampsia and eclampsia were treated with regional nerve block anesthesia. In 1943, Hingson and Edwards[3] reported the use of caudal anesthesia in the management of twelve patients with severe toxemia of pregnancy. These authors described the following observations:

1. There was a slow progressive blood pressure fall, frequently amounting to 100 mm. of mercury within one hour. Associated with this reduction in vascular tension there was a warming, blushing, and drying of the lower extremities similar to that following bilateral lumbar sympathectomy.

2. There was an increase in the urinary output with a reduction in the concentration of the urine. We explain this phenomenon by the suggestion that the sympathetic nerve supply to the kidneys was blocked, with the corresponding maximum dilatation of the glomerulus and afferent arterioles.

3. Convulsions were controlled without resort to other forms of sedation.

4. The mental cloudiness of these patients cleared remarkably, they became more cooperative and three of them were able to take fluids and small servings of food.

5. There was no appreciable change in the heart rate of the fetus, and all of them were delivered without mortality or unusual postpartum morbidity.

At the Medical College of Virginia Hospitals difficulty has been experienced with the use of caudal anesthesia. With the patient in an unconscious state it was difficult to determine the proper time for injections of maintenance doses of the anesthetic agent. Once the level dropped too low, it was almost impossible to re-establish the required level of anesthesia. After a duration of twelve to fifteen hours the required level of anesthesia could not be maintained. Since most of our cases required anesthesia over a longer period of time, we changed to continuous spinal anesthesia.

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

Continuous spinal anesthesia had several advantages. After it had been started it could be continued for days, if necessary. Only small amounts of anesthetic agent (Metycaine 1.5 per cent) were needed to produce the desired effect.

Early in 1948 we decided to alter the plan of treatment of pre-eclampsia and eclampsia. Because of the excellent results obtained with continuous spinal anesthesia, the method now in use was selected. Twenty-four patients have been treated with continuous spinal anesthesia since this technique has been adopted. Twelve of these patients had severe pre-eclampsia and twelve had eclampsia with convulsions.

Material

The Medical College of Virginia Hospitals serve a large rural area and it is natural to expect a high percentage of abnormal cases. Prior to admission to the hospital most of these patients had either no prenatal care or inadequate care. All of the patients were admitted to the ward service.

The use of continuous spinal anesthesia was withheld only when there was a definite contraindication to its use.

Table I shows the racial incidence. This corresponds with the racial distribution in ward admissions.

TABLE I. INCIDENCE IN REFERENCE TO RACE

RACE	NO. OF CASES	PERCENTAGE
White	4	16.67
Negro	20	83.33
Total	24	100.00

Table II shows the age incidence. As expected, a large percentage of the patients were less than 20 years of age. Only one patient was over 30 years.

TABLE II. INCIDENCE IN REFERENCE TO AGE

AGE IN YEARS	NO. OF CASES
14 to 15	5
15 to 20	9
20 to 25	7
25 to 30	2
30 to 35	1
Total	24

Table III shows the incidence in reference to prenatal care. Most of the patients had been seen by a doctor before they were admitted to the hospital, but they had not reported regularly either to their physician or to a prenatal clinic.

TABLE III. INCIDENCE IN REFERENCE TO PRENATAL CARE

CARE	NO. OF CASES	PER CENT
Inadequate	21	87.5
None	3	12.5
Total	24	100.0

Table IV shows the incidence in reference to parity.

TABLE IV. INCIDENCE IN REFERENCE TO PARITY

PARITY	NO. OF CASES	PER CENT
Primiparas	19	79.1
Multiparas	5	20.9
Total	24	100.0

Table V shows the average, high, and low blood pressures at the time of admission to the hospital. The table clearly indicates the severity of both the pre-eclampsia and eclampsia.

TABLE V. BLOOD PRESSURE AT THE TIME OF ADMISSION

	HIGH	LOW	AVERAGE
Pre-eclampsia	210/140	175/95	181/116
Eclampsia	250/130	135/80	175/106

Table VI shows the incidence in reference to the convulsive seizures that occurred prior to admission to the hospital and also those that occurred after admission but before treatment with spinal anesthesia was started.

TABLE VI. CONVULSIVE SEIZURES

NO. OF CASES	CONVULSIONS PRIOR TO ADM.	CONVULSIONS AFTER ADM. PRIOR TO SPINAL	AVERAGE NUMBER CONVULSIONS PER PATIENT
12	78	24	8.5

Table VII shows the incidence of patients as related to antepartum, intrapartum, and postpartum groups.

TABLE VII. TYPE OF ECLAMPSIA

	ANTEPARTUM	INTRAPARTUM	POSTPARTUM	NO. BABIES
Eclampsia	8	2	2	11

Two of the patients with eclampsia were admitted to the hospital after delivery. Ten patients in this group were delivered in the hospital. One of these had twins.

Treatment

As soon as possible after admission the patient with a severe toxemia of pregnancy is placed in a quiet, darkened room. If she has severe pre-eclampsia or eclampsia (which was true of all of the patients reported in this paper), a continuous spinal anesthesia is started immediately.

An initial dose of 0.5 c.c. of 1.5 per cent Metycaine solution (7.5 mg.) is then injected. The blood pressure is recorded after five minutes and again after ten minutes. After the initial recordings the blood pressure should be obtained every fifteen minutes. Subsequent injections are given at fifteen- or thirty-minute intervals. As a rule, 0.5 c.c. at fifteen-minute intervals is all that is required. We never give more than 1 c.c. unless the patient is ready for delivery. The blood pressure readings will indicate the necessity for the frequency and the amount of solution required. The smallest amount that will produce the desired effect is the proper dose to use.

A venipuncture is done and blood drawn for the following determinations: a. blood sugar, b. nonprotein nitrogen, c. uric acid, d. carbon dioxide combining power, e. total and fractional proteins, f. type, Rh and cross matching of blood. The venipuncture needle is then strapped in place.

Intravenous fluids are then started through the needle already in place. The following solutions are given: a. 400 c.c. of 10 per cent dextrose solution in distilled water, b. 80 c.c. of sodium lactate solution, c. 1.2 mg. of digitoxin.

The intravenous fluids are allowed to run in slowly. A similar volume of dextrose is given every four hours until the patient can take the necessary amount by mouth. If a patient has anuria or a very limited urinary output, the volume of intravenous fluids is limited to 250 c.c. of 10 per cent glucose solution every four hours. If, after the initial blood chemistry is reported, the carbon dioxide combining power is below normal, additional sodium lactate is added to the subsequent dextrose injections. The patient should receive a maintenance dose of digitoxin (0.2 mg.) daily.

As soon as the blood pressure is controlled, the perineum is prepared for examination. A pelvic examination is done to evaluate the pelvis and to ascertain the condition of the cervix. At this time a Foley catheter is put in the bladder and it is drained every hour and the urinary output is recorded.

Special attention is given to the level of the anesthesia. It is not difficult to determine the level in a conscious patient. This is accomplished by testing the area of skin anesthesia. However, in the case of an unconscious eclamptic it is often quite difficult. In these patients the excursion of the intercostal muscles is observed closely. If there is any question about the level of anesthesia being too high further injections of Metycaine are discontinued until we are certain of the existing level.

Should the situation demand, the air passages are freed of mucus and nasal oxygen administered.

As soon as the patient becomes conscious and can cooperate, she is given 200 c.c. of sweetened fruit juice or water every hour.

When the patient is ready for delivery, additional anesthesia is needed. This is obtained by placing the patient in a sitting position and by injecting 2 c.c. of Metycaine slowly. This sitting position is maintained for thirty minutes. The level of anesthesia is then checked and, as a rule, it is adequate for delivery.

Results, Maternal

1. *Mortality.*—

Twenty-four cases were managed by the treatment outlined. There were no maternal deaths in this series.

2. *Control of Blood Pressure.*—

The blood pressure was immediately lowered. As was to be expected, it rose gradually toward its former level but was quickly relowered by subsequent injections of Metycaine. After several hours, larger doses of Metycaine are required to produce the desired effect. At this point, when possible, it was found to be best to discontinue injections for one hour. When the injections were resumed the desired effect was again produced. Table VIII shows the average blood pressure obtained at the time of admission and after the spinal anesthesia had been started. It also indicates the time and amount of drug required to control the cases in our series.

3. *Control of Convulsive Seizures.*—

The convulsive seizures were controlled. In our series of twelve cases of eclampsia only four seizures were encountered after the treatment had been started. One of these occurred five minutes after the initial injection was given. As indicated in Table VI, the twelve patients with eclampsia had a total of one hundred and two convulsions prior to spinal therapy. Control of the convulsions was thought to be due to the lowering of the blood pressure to a near-normal level and to the removal of stimuli incident to the pains of labor.

TABLE VIII. BLOOD PRESSURE ON ADMISSION AND AVERAGE AFTER SPINAL ANESTHESIA; DURATION OF SPINAL ANESTHESIA AND AMOUNT OF METYCAINE REQUIRED

CASE	BLOOD PRESSURE		DURATION OF SPINAL (HOURS)			METYCAINE IN MG.
	ON ADMISSION	AVERAGE WITH SPINAL	PRIOR TO DELIVERY	AFTER DELIVERY	TOTAL	
Pre-eclampsia.—						
S. P.	170/100	140/ 90	66	3	69	750
D. W.	210/140	150/100	9	6.5	15.5	525
E. H.	170/120	130/ 90	29	28	57	420
B. J.	210/110	140/ 90	55	26	81	1,200
M. G.	175/ 95	140/ 80	8.5	23	31.5	375
J. H.	160/105	150/ 90	2.25	17.75	20	450
A. M.	200/135	150/100	34	42	76	2,310
H. P.	165/130	130/ 90	24	0	24.5	210
L. R.	165/105	140/ 90	11	2.5	13.5	300
I. S.	170/110	140/ 90	8	28	36	405
J. C.	190/130	120/ 80	5	2	7	150
C. R.	190/120	160/100	124	15	139	1,470
Average	181/116	141/ 91	31.3	16.1	47.4	713
					(Total	8,565)
Eclampsia.—						
S. P.	190/120	140/ 90	3	9	12	255
J. W.	170/120	140/100	24.5	0	24.5	900
E. M.	135/ 80	110/ 80	28	17	45	750
D. B.*	165/120	120/ 80	0	28	28	255
M. M.	170/ 90	140/100	45	14	59	1,305
S. W.	170/120	140/ 90	15.5	30	45.5	1,695
A. C.	150/120	120/ 90	12	13	25	375
G. C.	170/120	140/ 90	60	24	84	2,250
E. J.	148/114	140/ 90	52	0	52	1,125
M. D.	250/130	150/100	62	42	104	1,465
M. R.	200/100	150/ 90	86	1.5	87.5	1,965
B. J.*	180/100	160/100	0	52	52	1,010
Average	175/106	136/ 91	32.33	19.2	51.5	1,112
					(Total	13,350)

*Postpartum admissions.

4. *Improvement of Urinary Output.—*

The urinary output was restored to a normal level. Hingson and Edwards attribute this to the removal of sympathetic influences thereby giving a maximum of glomerulus and afferent arterioles. It required approximately twenty-four hours to restore the output to normal proportions. Frequently, the output exceeded 4,000 c.c. for twenty-four hours and in one case it exceeded 9,000 c.c. during a similar period of time.

Six of the patients had an oliguria. Five of these were restored to normal within twelve hours; the sixth was restored in twenty-four hours.

5. *Pulmonary Edema.—*

This complication did not occur. Its absence was attributed to two things. As previously stated, these patients were all digitalized at the time they received their initial intravenous fluids. We are convinced that this procedure is very important in handling this type of patient, since nearly all of these patients have some degree of heart failure. The spinal anesthesia creates a "bloodless phlebotomy." This lessens the load on a heart that is greatly overtaxed, by pooling blood in splanchnics and lower extremities.

6. *Labor and Deliveries.—*

The presence of the continuous spinal anesthesia gave us an ideal analgesia during labor. It was because of the absence of pain, usually associated with

labor, that we were able to keep these patients quiet, comfortable, and removed from stimuli which frequently initiate convulsions. The anesthesia did not seem to either retard labor in progress or prevent induction of labor when it was indicated.

The deliveries were completed under the spinal anesthesia. The comparatively weak solution used provided only a segmental anesthesia and it was necessary to obtain additional anesthesia, as described in our technique. The anesthesia was entirely satisfactory for both vaginal and abdominal deliveries.

Table IX shows the incidence of types of delivery and fetal result. There were two multiple pregnancies (twins) in our series. As two patients were post partum at the time of admission, their babies are not included in the table. The indications for cesarean section are given and incidence of stillbirths is explained.

TABLE IX. INCIDENCE OF TYPES OF DELIVERY AND FETAL RESULT

TYPE OF DELIVERY	NO. DEL.	FETAL RESULT
Spont. vaginal delivery	6	6 live births
Forceps delivery	9	9 live births
Breech extraction	2	2 stillbirths
Version and extraction	1	1 stillbirth
Cesarean section	5	5 live births
Hysterotomy	1	1 stillbirth
	24	20 live births; 4 stillbirths

IXA. Indications for cesarean section were:

a. Fibroids obstructing birth canal	1
b. Interruption after control of the toxemia	2
c. Primary uterine inertia	1
d. Premature separation of placenta	1
	5

IXB. Indication for hysterotomy was:

a. Interruption of pregnancy of 24 weeks complicated by eclampsia	1
	1

IXC. Stillbirths:

a. Macerated twins, weighing 7 pounds, 3 ounces and 7 pounds, 7 ounces, were delivered in the case of E. M. There were no fetal heart tones present at the time of admission	2
b. In the case of M. G. the baby was alive just prior to delivery as evidenced by the presence of fetal heart tones. The baby was delivered by breech extraction and was stillborn. Weight, 7 pounds, 1 ounce	1
c. Hysterotomy was performed in the case of M. D. for the interruption of a pregnancy of 24 weeks' duration. This produced a stillborn fetus weighing 610 grams	1
	4

IXD. Neonatal Deaths:

a. A living baby which weighed 7 pounds, 11 ounces was delivered to A. C. with low forceps. The condition of the baby at the time of delivery was thought to be only fair. After four and one-half hours the temperature rose to 105° F. All attempts to lower the temperature failed and the baby died twelve hours after delivery	1
	1

7. *Additional Sedation.*—

Before the effect of the spinal anesthesia can be properly evaluated, the additional sedation that was used in conjunction with it must be considered. One must also consider the amount and the frequency of each drug required for additional sedation. Small doses of Nembutal were used to combat any toxic effect of the Metycaine.

Before delivery the twenty-four patients were under continuous spinal anesthesia for a total of seven hundred sixty-three hours. During that period of time the twenty-four patients received a total of thirty-three doses of Nembutal, grains 1½, or an average of 1½ grains every 22.8 hours. In addition, the twenty-four patients received thirty-five hypodermic injections of Dilaudid, each injection $\frac{1}{32}$ grain. Dilaudid was administered when the patient became restless. It was given on an average of once every twenty-one and one-half hours to each patient.

After delivery we do not hesitate to use Dilaudid freely if the urinary output is normal. We usually give it every four hours during the first postpartum day. During the next twenty-four hours, it is given every six hours and discontinued altogether on the third postpartum day.

8. *Complications.*—

There were no complications incident to the use of spinal anesthesia. We think that this is particularly significant, since it will seldom be necessary to continue treatment for a longer period of time than was used in some of our cases.

One of our patients, an eclamptic, had a severe postpartum hemorrhage. The bleeding was controlled by packing the uterine cavity with gauze. She received a total of 2,000 c.c. of blood. There was no delay in obtaining whole blood as the patients were all Rh and group typed at the time of admission to the hospital.

Three patients had an elevation of temperature above normal during the puerperium. This was attributed to endometritis. All cases cleared up promptly and the patients were discharged in ten, twelve, and fourteen days, respectively.

One patient with eclampsia, upon whom a cesarean was performed, had a disruption of her operative wound. This required a prolonged hospital stay. She was discharged on her twenty-seventh hospital day.

There were two patients with postpartum eclampsia. One of these patients developed a postpartum psychosis on her sixth hospital day. She became so violent that it was necessary to commit her to an institution.

Results, Fetal

Fetal anoxia caused by heavy sedation with opiates and barbiturates was not encountered. These drugs were used sparingly and discontinued altogether when delivery was expected within six hours.

The babies were spared the long periods of anoxia brought about by convulsive seizures of the mother. This was borne out by the relatively good condition of most of the babies at the time of delivery.

The incidence of stillbirths and neonatal deaths with the proper corrections appears in Table X. The reasons for correction have already been given in Table IX.

TABLE X. INCIDENCE OF STILLBIRTHS AND NEONATAL DEATHS

	NO.	PERCENTAGE
Stillbirths	4	16.66
Corrected	1	4.16
Neonatal death	1	4.16
Total fetal mortality	2	8.32

Summary and Conclusions

A report of twenty-four cases of severe pre-eclampsia and eclampsia has been presented. Twelve of the patients had convulsive seizures.

1. Maternal mortality in severe pre-eclampsia and eclampsia can be lowered by the use of continuous spinal anesthesia. There were no deaths in twenty-four cases of severe toxemia reported in this paper.

2. Fetal mortality can also be lowered by this plan of treatment. The corrected fetal mortality was 8.32 per cent, and the gross fetal mortality was 16.66 per cent.

3. Convulsive seizures were adequately controlled. Only four convulsions occurred after treatment with continuous spinal anesthesia was started.

4. The patients are easier to handle because they are conscious and are able to cooperate.

5. Continuous spinal anesthesia is an aid in restoring a normal urinary output.

6. Adequate anesthesia for both vaginal and abdominal deliveries was obtained.

7. No complications incident to the use of spinal anesthesia were encountered in this series of twenty-four patients.

8. Our series of cases is still small but we think it definitely indicates that spinal anesthesia should be further investigated in the treatment of pre-eclampsia and eclampsia.

References

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Discussion

DR. WM. DURWOOD SUGGS, Richmond, Va.—In so far as I am aware, this report on the treatment of severe eclampsism represents pioneer work in this field. However, as mentioned, Hingson and Edwards in 1943 utilized the same general principles and accomplished much the same results employing continuous caudal anesthesia.

Theoretically, any relatively safe procedure which will reduce and maintain blood pressure at a lowered level, diminish external stimulation, increase urinary output, and improve circulatory stability without any depressing or other untoward effect upon the fetus until it can be delivered, would be ideal. Continuous spinal anesthesia, as employed in the twenty-four cases reported, or caudal anesthesia, seems to meet these requisites to a large degree. In addition, spinal anesthesia provides a most satisfactory anesthesia for delivery without danger of anoxia to the mother or fetus, provided the blood pressure is not permitted to drop too low. I am in agreement with the authors that continuous spinal would be safer and more practical than caudal anesthesia in the hands of most of us.

Lumbar puncture per se will reduce blood pressure in 50 per cent of pre-eclamptic and eclamptic patients according to Wieloch. He found increased intraspinal pressure, which he attributed to cerebral edema, and removed 50 c.c. of fluid. This was followed by diuresis in 38 per cent of cases.

Lundy and others have demonstrated experimentally that the fall in blood pressure is due to the blocking of the sympathetic nerve supply to the vessels below the anesthesia level. This vascular relaxation undoubtedly promotes diuresis and drains blood into the visceral vessels where it remains available to the general circulation instead of being lost as in phlebotomy.

Although the excellent results from both the maternal and fetal standpoint in this series can probably be attributed to a large degree to skillful use of continuous spinal anesthesia, the conjunctive measures employed are also important. I am inclined to feel

that the volume of intravenous fluids employed (2,400 c.c.) is excessive and would restrict the intake by 50 to 60 per cent in the presence of edema. The value of rapid digitalization was suggested by Dr. M. Pierce Rucker in January, 1931, and in subsequent reports and is widely used in Richmond and elsewhere. It probably reduces the incidence of circulatory collapse and pulmonary edema and thus secondarily improves urine output.

Vara, Paavo: Studies on the Elderly Primipara, Acta obst. gynec. Scandinav., vol. 26, supplement 2, 1946.

Vara reviews the obstetrical histories of all elderly primiparas delivered at the Women's Clinic of Helsinki in the 15-year period from 1927 to 1941, inclusive. In this group he included women aged 30 or more who were delivered of progeny weighing 600 Gm. or more. In this period there was a total of 41,634 deliveries and among these were 19,216 primiparas. Primipara cases in the ages of 30 to 34 years numbered 2,592; 35 to 39 years, 778 cases; and 40 years old or more, 197 cases—or a total of 3,567 elderly primiparas as classified by age groupings only. In 1927 the elderly primiparas appeared as about ten per cent of those bearing their first children, while in 1941 the elderly primipara was found as 25 per cent of the total primipara group of that year.

The author has a wealth of valuable and detailed data in his 133-page monograph. Only that thought most pertinent to American readers can be included in abstract form. Breech presentation was found in an incidence of 3.38 per cent. Contracted pelves, 6.42 per cent, was a similar figure to the younger group of primiparas. The operative incidence of full-term deliveries in cases with normal pelves was 22.4 per cent (forceps 12.5 per cent; section 4.2 per cent; other methods 5.7 per cent).

The incidence of postpartum infection was no greater in the elderly primiparous group, 15.3 per cent. Primary inertia was found in 6.8 per cent and secondary inertia in 18.2 per cent, an incidence nearly double that of the younger primipara group.

Hemorrhages were no more frequent in the older cases although soft-part ruptures were increased, first degree, 43.4 per cent; second degree, 14.2 per cent; and third degree tears, 0.7 per cent.

Maternal mortality was 0.12 per cent in spontaneous delivery group; 4.1 per cent in the operative group. The latter group showed 4.9 per cent after section and 0.7 per cent after forceps delivery. These figures were "probably" higher than in younger group.

The average weight of the babies was 3.561 Gm. The sex ratio of boys to girls in all the group of elderly primiparas was 107.05 to 100 while in women with first babies after 40 years of age the sex ratio of boys to girls was 136.6 to 100. Asphyxia was found in 7.36 per cent of deliveries. Fetal mortality was greater, 3.07 per 100. Prematurity was found in 8.52 per cent of deliveries.

The author divides his elderly primiparas into two interesting constitutional groups, (1) fully normal, and (2) presenile group. He then breaks these down into constitutional types and arrives at a new approach (probability calculus) to statistical analysis in this aspect, e.g., he found shorter and stouter women were more frequent in the operative group. This same type also had a later menarche, 15.4 years, as compared to younger primiparas.

Vara found artificial rupture of membranes done twice as frequently in the elderly group. He concludes that in addition to age factors or other complications in elderly primiparas the obstetrician must examine and manage carefully the constitutional characteristics of this group. He states the older primipara must absolutely be hospitalized. Twenty-five tables are contained in this valuable study. CLAIR E. FOLSOME.

PROLONGED LABOR*

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(From the Bradford Clinic)

PROLONGED labor is a progressively serious obstetrical problem fraught with maternal hardship, suffering, and potential injury. Most obstetrical texts list this entity as one of the more important predisposing causes of postpartum hemorrhage and puerperal infection, while numerous articles have been written concerning the conduct of such labor and the many factors that may contribute to a prolongation of the process of parturition. The actual delivery following a prolonged labor frequently calls for the best in obstetrical judgment and technique, both as to timing of intervention and choice of operation, for among the latter are often encountered the most formidable surgical procedures in the field of obstetrics.

This presentation constitutes an analysis and critical evaluation of eighty-five cases of prolonged labor occurring in 2,634 consecutive deliveries of white patients in a private obstetrical practice. Three and one-third per cent of these patients were in labor over thirty hours and 0.85 per cent over fifty hours.

The inability to establish with accuracy the time at which labor was initiated influences materially the reported incidence of this problem. We have attempted to eliminate in this series all cases of uterine irritability, no matter how painful, prior to the onset of regular or productive contractions and hence have established a more rigid standard of duration of labor than might be necessary. Also, a reasonably militant policy has been adopted toward the problems of both primary uterine inertia and cephalopelvic disproportion, with abdominal delivery usually being elected in such cases following trial labor of less than fifteen hours in the absence of engagement. The surgical approach to the dystocia patient earlier in labor has served to reduce the incidence of patients in labor over thirty hours in this series. The consistency of medical supervision in the hands of the authors is a contrast to larger types of clinic practice where varying attitudes toward the problem of dystocia might be adopted on different services or where even on the same service a prolonged labor problem might be handled by changing shifts of physicians.

Table I. Age Group

Under 20 years	10	12%
20 to 29 years	44	53%
30 to 39 years	31	35%
40 years	0	

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

There is no striking relationship between age and prolongation of labor in these patients. The incidence is well divided between patients in all ages of the reproductive period of life with the exception that no patient over 39 years of age was permitted to remain in labor over thirty hours.

TABLE II. METHOD OF DELIVERY

	PRIMIPARAS	MULTIPARAS	TOTAL
Spontaneous	3	5	8
Low forceps	18	7	25
Midforceps	36	4	40
Breech extraction	2	0	2
Cesarean	9	0	9
Fetal mutilation (24 weeks' gestation)	0	1	1
Total	68	17	85

There were 68 primiparas and 17 multiparas in this series. Ninety-five per cent of the primiparas eventually required an operative delivery, usually a procedure of serious difficulty, requiring evaluation and decision as to the method of greatest safety and instrumentation of the least trauma. While the history of successful vaginal delivery did not insure the physiological progress of all subsequent labors, nevertheless delivery was eventually accomplished either spontaneously or by low forceps in twelve of the seventeen multiparas.

TABLE III. MAJOR SURGICAL INTERFERENCE

	PRIMIPARAS (68)	MULTIPARAS (17)
Midforceps	56%	24%
Breech extraction	3%	0
Cesarean	13%	0
Fetal mutilation	0	6%
Total	72%	30%

The third table reveals an amazingly high incidence of major operative interference following prolongation of labor. In 72 per cent of the primiparas delivery necessitated either section, difficult midforceps or breech extraction. The one destructive operation was upon a nonviable fetus following 120 hours of labor in a multipara. It is obvious from a study of Tables II and III that the prolongation of labor, particularly in primiparas, did not solve the problem of delivery but in a high percentage of cases the passage of time presented the accoucheur with a surgical entity of major degree.

TABLE IV. CONTRIBUTING CAUSES OF PROLONGED LABOR

Cephalopelvic disproportion	40	(49%)
Occiput posterior	50	(62%)
Primary inertia	21	(26%)
Breech presentation	4	(4.7%)
Surgical induction	12	(14%)

Outstanding among the factors that might be regarded as leading to a prolongation of labor are disproportion and uterine inertia. The former was noted in nearly 50 per cent of the vertex presentations but obviously was not regarded as severe early in labor. An occiput posterior position, or transverse arrest, occurred in 50 of the 81 vertex presentations, or 62 per cent.

This emphasizes the high incidence of disturbance of normal fetal-pelvic relationship and mechanics of parturition when labor is prolonged. However, early descent of the vertex in midpelvis and the frequent use of x-rays usually gave a favorable prognosis as to ultimate delivery per vaginam. Conversely, failure of engagement usually led to recognition of more severe degrees of dis-

proportion, and section before labor became seriously prolonged. In this connection the use of x-ray pelvimetry has been of very limited value in prognosis. However, the correlation of radiologic study of the pelvis with clinical evaluation of cephalopelvic relationship, the type of labor, condition of the cervix, and other individual factors that are involved in every case of disproportion has been the usual method of obstetric deduction in this series.

Primary uterine inertia was noted in 21 cases (26 per cent). This type of desultory labor was treated by various methods including fractional Pituitrin, artificial rupture of the membranes, intravenous calcium, sedation, and general supportive measures. It is our impression that when pathological forces of this type have been in evidence for over thirty hours an establishment of frequent, regular, and productive contractions is unusual. Those patients who respond more satisfactorily to accepted methods of treatment of uterine inertia are usually delivered under thirty hours. The longer the labor the less responsive the uterus becomes to all efforts to develop the physiologic process of parturition.

The incidence of breech presentation in this series is not significant. Undoubtedly the recognition of pelvic contraction, pathological cervical dilatation, or uterine inertia when associated with a breech presentation should usually lead to delivery by section before thirty hours of labor. The four cases in this group all occurred in primiparas, two being delivered by section and two by extraction.

As a contributing cause to the prolongation of labor, surgical induction has probably not been adequately considered. Twelve patients (14 per cent) had such induction by artificial rupture of membranes, eight for toxemia and four for elective reasons. While it is granted that this complication may be reduced to a minimum by clinical evaluation of the potential labor and desisting from induction in the presence of an unfavorable cervix, or oligohydramnios, or abnormalities of presentation, nevertheless, the fact that eight cases of surgical induction for pregnancy toxemia were in labor for over thirty hours (not including the latent period following rupture of membranes) should be thought provoking. The unpredictable labor that may follow surgical induction has led to a more generous employment of abdominal section, especially in fulminating preeclampsia that does not improve promptly under medical therapy.

TABLE V. DURATION OF LABOR AND MORBIDITY

HOURS	CASES (85)	MORBID (15%)
30- 39	42	5 (12%)
40- 49	21	3 (14%)
50-120	22	5 (23%)

There were no severe cases of puerperal infection in the series although 20 patients were febrile during labor and 13, or 15 per cent, had puerperal morbidity (100.4° F. in any two twenty-four-hour periods following delivery). Prophylactic penicillin and sulfonamide were given to a portion of these patients as in recent years it has become our policy to administer these drugs to parturients with prolonged rupture of the membranes or prolongation of labor. The incidence of morbidity is somewhat increased as labor becomes more prolonged, although the relation of this observation must be correlated with the increased operative problem that also develops as seen in the next table.

TABLE VI. DURATION OF LABOR AND MAJOR OPERATIVE DELIVERY

HOURS	NO. OF CASES (85)	MIDFORCEPS OR CESAREAN (60%)
30- 39	42	20 (48%)
40- 49	21	11 (53%)
50-120	22	19 (85%)

The difficulties and dangers of delivery were directly proportionate to the duration of labor. Of 22 patients in labor over fifty hours, 19, or 85 per cent, had complicated and difficult operative deliveries, i.e., midforceps, destructive operation on fetus, or cesarean. Among 12 patients in labor over sixty hours (the maximum being 120 hours of labor in two instances) there were 10 exceedingly difficult operative terminations including two sections. Comparing this with an incidence of 60 per cent in the entire group of 85 patients an incidence of 48 per cent in those laboring between thirty and thirty-nine hours, the striking increase of major operative surgery for eventual delivery as labor becomes more and more prolonged is apparent.

TABLE VII. DURATION OF LABOR AND INCOMPLETE CERVICAL DILATATION

HOURS	NO. OF CASES	INCOMPLETE DILATATION OF CERVIX
30- 49	63	9 (14%)
50-60	10	4 (40%)
60-120	12	9 (75%)
Total	85	22 (26%)

The cervix failed to dilate completely in 22 patients, over one-fourth of the total number. Eight of these were eventually delivered by cesarean section and fourteen per vaginam. It is a significant fact that the incidence of failure to dilate increases directly with the duration of labor. After fifty hours 60 per cent failed ever to accomplish cervical dilatation and of those in labor over sixty hours 75 per cent were eventually delivered undilated. In such cases "more labor" will seldom accomplish dilatation. In this series of cases the problems of delivery were very rarely solved or made simpler by permitting labor to continue over fifty hours.

TABLE VIII. INFANT MORTALITY

Term deliveries	79		
Prematures	6		
Sets of twins	3		
Total infants		88	
Stillbirths		2	
Neonatal deaths		2	
Corrected infant mortality		1	(1.1%)

One stillbirth occurred in the course of a destructive operation on a six months' fetus following 120 hours of labor. The second was a full-term child, lost during a difficult forceps extraction. This case was regarded as an error in judgment in failing to section late in labor. One neonatal death occurred from prematurity at 6 months and the second was a hydrocephalic that survived several hours following craniotomy.

There were 84 infants discharged from the hospital living and apparently well. The corrected infant mortality of only one in 85 cases of prolonged labor (1.19 per cent), in spite of the attendant complications of delivery as previously tabulated, was most surprising. Secondary to unusually good fortune numerous factors have contributed to this result including prenatal care, support during labor, selective analgesia and anesthesia, choice of operative delivery, and constant obstetrical supervision by the attending physician.

TABLE IX. MATERNAL COMPLICATIONS

Maternal deaths	0	
Postpartum hemorrhage	0	
Morbidity	13	(15%)

The incidence of postpartum hemorrhage and puerperal infection has generally been accepted as high following prolongation of labor. Such was not our

experience. There were no cases of postpartum hemorrhage. One patient with a twin pregnancy had a delayed hemorrhage at home two weeks following delivery and one patient had moderately severe bleeding from soft tissue injury sustained during a difficult forceps extraction.

In this connection the prophylactic intravenous administration of ergonovine as the vertex is delivered has been most effective in reducing hemorrhage in the third stage of labor. Prompt placental separation usually follows and excellent postpartum uterine contraction without bleeding is thereby maintained. In those cases where the placenta fails to separate promptly or becomes trapped in the cervix, manual removal is immediately accomplished. In the series of 85 cases no perineal repair was commenced prior to complete delivery of the placenta and no patient required intrauterine packing post partum.

The incidence of morbidity which has previously been discussed in its relation to duration of labor and operative delivery is not strikingly high, 15 per cent. Vaginal examinations were necessary during labor in nearly two-thirds of the cases. No routine intravaginal instillations were employed.

Cesarean Section

There were nine cesarean sections in the 85 deliveries, an incidence of 10.6 per cent. Seven were delivered by the transperitoneal route and two were extraperitoneal. All were in primiparas, two with breech presentations, and there were no serious postoperative complications in the group. One neonatal death occurred in the hydrocephalic reported, which case was referred from a near-by city following prolonged labor.

Abdominal delivery was probably not employed as liberally as might have been indicated in view of the additional safety of the extraperitoneal operation following prolongation of labor. There are several cases here reported as delivered by difficult midforceps that would have been better handled by cesarean section and would be so handled today in the light of broader experience and more familiarity with the extraperitoneal operation.

Discussion

The conduct of pregnancy, labor, and delivery becomes of the utmost importance when the process of parturition becomes prolonged. These private patients were for the most part in excellent condition at the onset of labor, having received and cooperated with an intensive prenatal care program. In addition to physical preparation for labor, the psychic and emotional attitude was usually good, fear complexes were at a minimum and confidence in the medical attendant was usually present. The value of this status in a patient with dystocia and prolongation of labor cannot be overemphasized.

The conduct of these labors was along accepted patterns of support and prophylaxis. Fluids in abundance by mouth and vein, together with adequate intervals of rest were supplied. In this connection morphine, either alone or following small dosage of barbiturates, was administered to 61 of the 85 patients. Demerol was used in only nine of these patients. It is our impression that the short-lived action of Demerol limits its usefulness in prolonged labor and that the restlessness and general physical depression following large and repeated doses of barbiturates preclude their continued use after labor becomes prolonged. Accordingly morphine, in adequate and repeated dosage, supplemented frequently with scopolamine, has continued to be the analgesic of choice in prolonged labor. Delivery has generally been accomplished under cyclopropane but

occasionally under nitrous-oxide-ether anesthesia. Neither caudal nor spinal anesthesia was administered to any patients following prolongation of labor.

By far the most common surgical problem encountered was that of transverse arrest of the occiput. The Barton forceps has proved to be a most acceptable instrument for delivery in this condition. Usually a biparietal application can be obtained by which further descent and rotation may be accomplished without dangerous trauma. This forceps is frequently removed following rotation and Piper axis traction forceps applied with which heavier traction can be exerted.

In the more severe disproportion problems with much moulding and possible impaction of the vertex in the transverse position delivery may be accomplished more readily with the Kielland forceps. No cases of failed forceps occurred in this series of 85 deliveries, but there were a number of cases of error in judgment that might better have been subjected to extraperitoneal section, without persistent although usually successful efforts to accomplish delivery per vaginam.

Summary

1. In an analysis of 2,634 consecutive deliveries of white patients from a private obstetrical practice it was found that labor was unduly prolonged in 85 cases, persisting longer, than thirty hours in 3.3 per cent and more than fifty hours in 0.84 per cent of the patients.

2. Midforceps, breech extraction, or cesarean section was necessary for delivery in 72 per cent of primiparas and 30 per cent of multiparas following such prolongation of labor.

3. After fifty hours of labor progress occurred with diminishing frequency, midforceps, destructive operation, or section being necessary in 85 per cent, and undilated cervices persisting in 60 per cent of such cases.

4. No case of postpartum hemorrhage or serious puerperal infection occurred.

5. In this series of 85 cases of prolonged labor only one viable, normal baby was lost (1.1 per cent), and there was no maternal mortality.

6. The low incidence of postpartum complications and the satisfactory infant and maternal results herein presented indicate that prolonged labor can usually be managed successfully. However, after fifty hours of labor interference should seldom be further delayed and extraperitoneal cesarean section should be more liberally employed.

1509 Elizabeth Avenue

UTERINE MUSCLE PHYSIOLOGY FROM LABORATORY TO BEDSIDE, A TREACHEROUS CROSSING*

WILLIAM BICKERS, M.D., AND MARIBELLE WOODS, M.S., RICHMOND, VA.

OUR knowledge of endocrinology and indeed all human physiology rests largely upon the conclusions drawn from experimentation with the lower animals. The clinician must yet rely upon phylogenetic forms lower than man for the advancement of his diagnostic and therapeutic endeavors. The uncritical manner in which clinicians accept the conclusions of the animal laboratory implies the presence of a broad and easily traversable span between animal and human physiology. The span is at least in part a mythical structure and grave error occurs when the conclusions of laboratory experiments along with the laboratory interpretation are brought uncritically to the bedside. The hiatus is a real one and the danger of such analogies should from time to time be brought to the attention of the physiologists and clinicians.

Satisfactory methods are now available for studying human and animal uteri in situ, thus providing a means for direct comparison of endocrine effects upon the myometrium. Perhaps no sphere of human therapy is more confused than that of endocrine therapy, particularly in relation to the human uterus. Endometrial response secondary to stimulation by the ovarian steroids in mammals is relatively constant and predictable. There are some differences resulting from the wide variations which exist in the end-artery structure of various endometriums. However, when one considers the hormones and their effect upon the myometrium as measured by uterine contraction patterns, there is little or no parallel to be found among the mammalian species.

From the clinician's viewpoint this is a problem of the first magnitude. The accommodation of the uterus to pregnancy, abortion, premature labor, parturition, expulsion of placenta, puerperal hemorrhage, uterine inertia, dysmenorrhea —to call the list of clinical syndromes related to disturbances in myometrial function is to recall our ignorance of the etiology and treatment of clinical syndromes related to myometrial dysfunction. If our understanding is to advance, we must first clear the decks of confusion and unrelated knowledge. As a starting point the comparison of animal and human uterine response to certain of the endocrines is worthy of interest.

Hormones and the Human Myometrium

The intact human uterus has an intrinsic motility which can be demonstrated. An intrauterine balloon, connected through a closed water system to a writing point, will record the uterine contractions upon a revolving kymograph.[1]

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

During the first half of the cycle, while the human uterus is under the influence of estrogen alone, the uterine contractions are of low amplitude, occur at a rate of two or three per minute and are relatively hypertonic. This pattern of motility is an intrinsic biological phenomenon related to the pituitary-ovarian cycle.[1, 2]

Estrogen-Progesterone Effects.—Following bilateral oophorectomy the uterus loses its intrinsic motility and becomes passive which indicates the essential role played by the ovarian steroids in uterine muscle physiology.[1] The pattern of uterine motility can be restored by the cyclic administration of estrogen and progesterone in doses simulating their endogenous production by the normal ovary (Fig. 1).

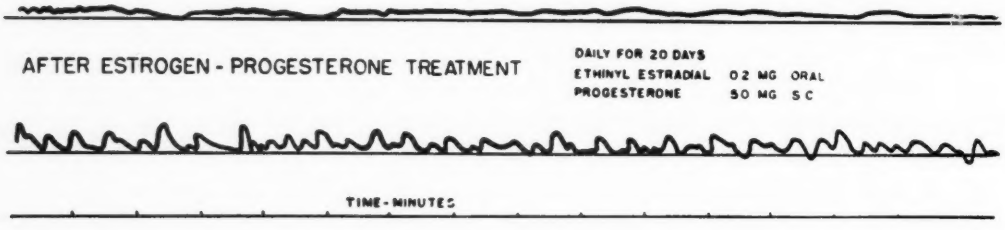
AFTER ESTROGEN - PROGESTERONE TREATMENT
DAILY FOR 20 DAYS
ETHINYL ESTRADIAL 0.2 MG ORAL
PROGESTERONE 50 MG S.C.
TIME - MINUTES

Fig. 1.—Castrate woman. Uterus is noncontractile. After estrogen-progesterone treatment the normal type of postovulatory human uterine contractions were induced.

In the patient with an intact uterus and normally functioning ovaries, the administration of estrogens does not alter the pattern of contractility during the first half of the cycle. However, if the estrogen be administered in sufficiently large doses, 5.0 mg. of stilbestrol daily throughout the cycle, ovulation will be inhibited, no corpus luteum will be formed, and the estrogen type of contractions persists. The estrogen contractions can be altered by the administration of progesterone in sufficiently large doses, 20.0 mg. daily for at least five days. It must be remembered that estrogen and progesterone are neither stimulating nor inhibitory to the myometrium in the sense that we usually construe these terms. There is a definite time interval during which the hormones must be administered (three to five days) in order to produce demonstrable effects; apparently a basic metabolic change is induced in the muscle fiber by hormone treatment.

Pitressin and Pitocin.[2, 5, 6, 7]—The nongravid human uterus reacts to the posterior pituitary principles in a very interesting and apparently paradoxical manner. During the first half of the cycle while the human uterus is under estrogen influence of the maturing follicle, the uterus is refractive to both Pitressin and Pitocin (Fig. 2). This passivity changes when the uterus comes under the influence of progesterone and estrogen (Fig. 2). During the last half of the cycle administration of Pitocin in a dose of 10 units intramuscularly occasionally induces a minimal fleeting oxytocic response, but more often has no effect upon the uterus. In contrast, the administration of Pitressin in a dose of 10 units intramuscularly during the postovulatory phase of the cycle invariably induces a marked hypertonicity and increased motility of the human uterus (Fig. 2). The myometrial spasm induced by Pitressin occurs in about three minutes after intramuscular injection and persists for a period of six to seventeen minutes. During this period of myometrial spasm the patient has all the clinical symptoms of severe dysmenorrhea. Never is Pitressin oxytocic to the uterus during the preovulatory phase, but it is invariably oxytocic during the postovulatory phase (Fig. 2). These effects of Pitressin on the human non-

gravid myometrium were first observed by Woodbury[2] and most of his observations are here confirmed. Progesterone is apparently necessary for myometrial sensitization to the vasopressor substance.

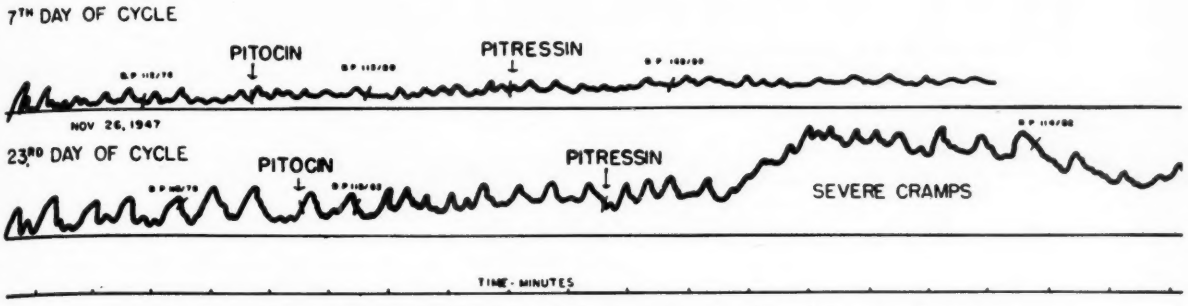

Fig. 2.—Human uterus during first half of cycle. Seventh day, normal estrogen contractions occur and uterus is refractory to Pitocin and Pitressin. During postovulatory phase of cycle, twenty-third day, contractions are normal progesterone type and uterus is relatively refractory to Pitocin, but highly sensitive to Pitressin.

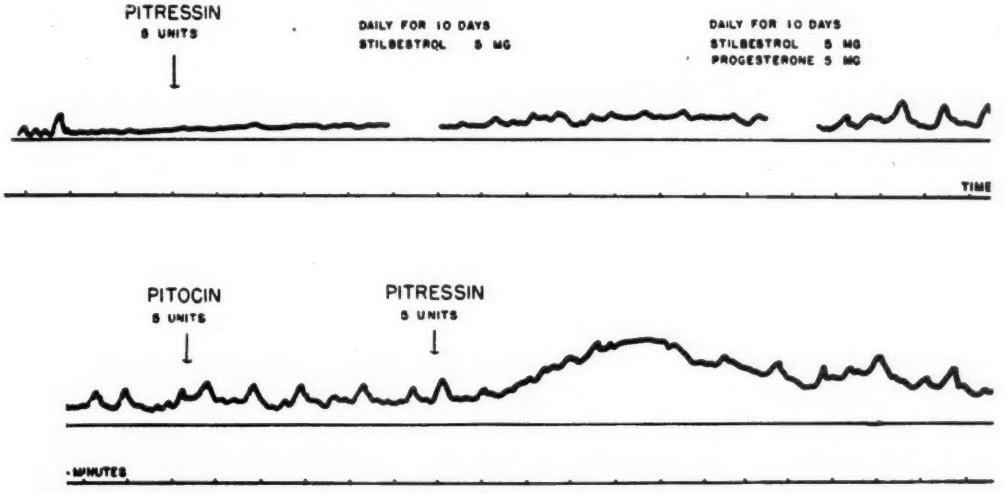

Fig. 3.—Castrate human uterus following stilbestrol-progesterone administration. Cyclic pattern of uterine contractions is induced and reaction to Pitocin and Pitressin is similar to that in the woman with intact ovaries.

The human castrate in whom all intrinsic uterine motility has been lost is refractive to stimulation either by Pitocin or by Pitressin (Fig. 3). However, if the castrate be given estrogen in the form of ethinyl-estradiol 0.2 mg. orally for twenty days and progesterone 10.0 mg. subcutaneously for ten days on the last ten days of estrogen administration, typical postovulatory type of estrogen-progesterone contractions is induced. Administration of Pitressin induces no response when given during the phase of estrogen administration alone, but it is strongly oxytocic when given during the period of estrogen-progesterone administration. This lends further evidence to the concept that progesterone is essential for the oxytocic effect of Pitressin and that it makes no difference whether the progesterone be endogenous or exogenous origin.

Hormones and the Rabbit Myometrium

Uterine contractions of the intact uterus have been studied in the urethane-anesthetized rabbit (4 c.c. per kilogram of body weight, 25 per cent solution

orally). The uterus is exposed and covered with saline and the rabbit is placed in a warm bath. A uterine horn is connected by means of a string to the recording apparatus, thus permitting observations of longitudinal contractions of the uterus in situ. The untreated rabbit uterus has an intrinsic motility; its contractions occur at the rate of two to three per minute (Fig. 4). It must be

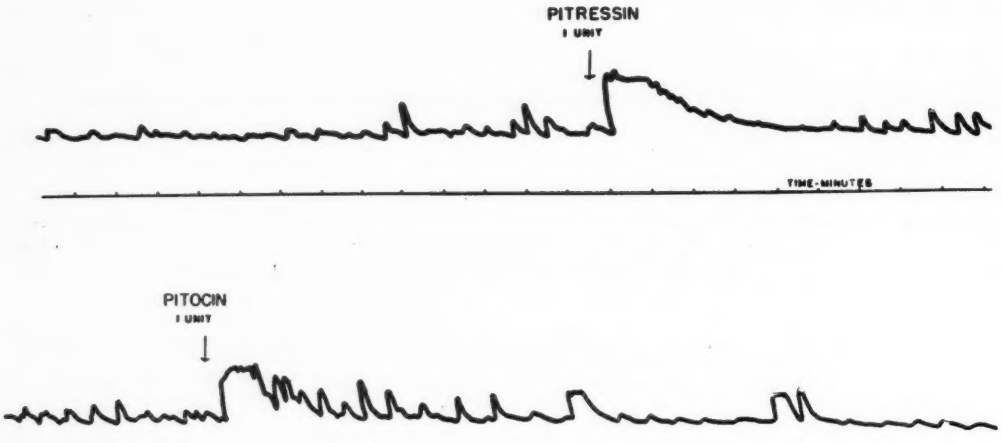

Fig. 4.—Rabbit uterus untreated. Intrinsic motility is shown. Reacts to Pitressin and Pitocin.

recalled that the rabbit, unlike the human being, is not subject to the cyclic estrogen-progesterone stimulation of the rhythmic pituitary-ovarian cycle. The rabbit ovaries are dormant and are aroused to ovulation only upon the stimulus of coitus or upon mechanical or electrical irritation. This factor places the rabbit uterus in an endocrine environment quite distinct from the human and it is not surprising that the response of the rabbit to the endocrines fails to parallel that of the human being. An estrogen (stilbestrol) was administered to rabbits in a dose of 1.0 mg. intramuscularly daily for seven days; the uterine motility was greatly augmented both in rate and in amplitude (Fig. 5). Simultaneous administration of stilbestrol (1.0 mg.) plus progesterone (5.0 mg.) daily for seven days in rabbits is followed by loss of uterine motility to the point where no contractions occur (Fig. 6). It has already been stated that the uterus of the human castrate under the influence of endogenous progesterone reacts in such a manner that the amplitude of contractions is increased while tonus and rate are reduced. Although contractions in the rabbit uterus are abolished by progesterone, the administration of this hormone to the human is followed by an increase in amplitude of the contractions and the rate is diminished. The almost unanimous acceptance of progesterone for the treatment of clinical syndromes associated with hyperirritability of the myometrium have resulted from this observation upon the rabbit uterus.[4, 8] There is no scientific basis for the use of progesterone in myometrial hyperirritability if it is given on the assumption that it inhibits uterine contractions, since progesterone does not reduce myometrial irritability in the human.

Effect of Pitocin and Pitressin.—The untreated intact rabbit uterus under urethane anesthesia is highly irritable to both Pitressin and Pitocin (Fig. 4). Both Pitocin and Pitressin administered intravenously in a dose of 1 unit to the rabbit are invariably followed by a marked oxytocic response. Now if the rabbit be given stilbestrol in a dose of 1.0 mg. intramuscularly daily for seven days,

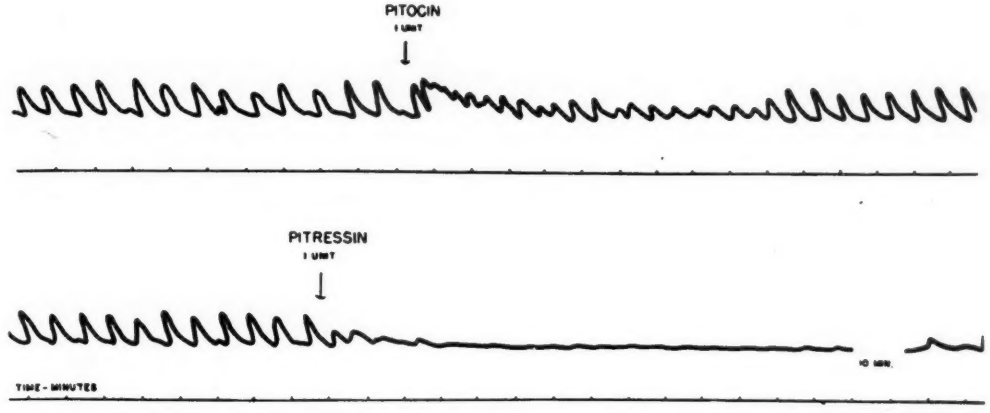

Fig. 5.—Rabbit uterus stilbestrol treated. Relatively refractory to Pitocin and completely inhibited by Pitressin.

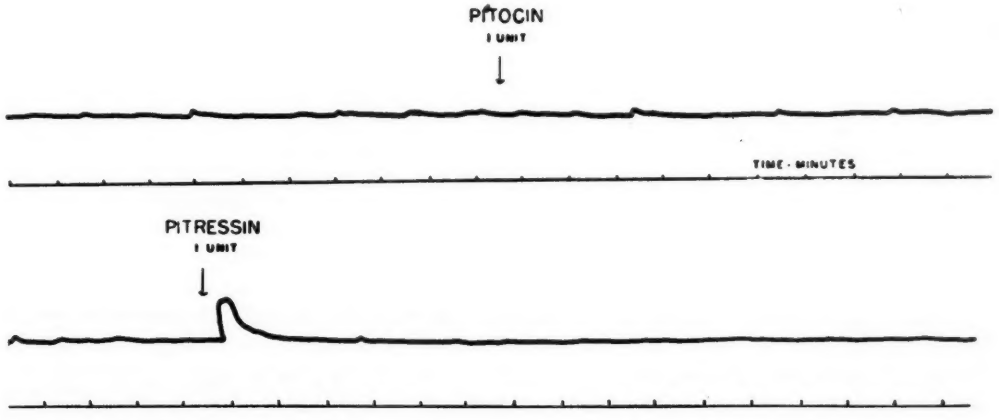

Fig. 6.—Rabbit uterus stilbestrol-progesterone treated. All uterine motility inhibited. Refractory to Pitocin and Pitressin.

there is no inhibition of uterine contraction, but its reaction to Pitocin is greatly reduced (Fig. 5). The administration of Pitressin is followed by a complete loss of motility (Fig. 5). This finding is so striking, namely, the complete obliteration of all estrogen-induced motility by Pitressin that the experiment was repeated time and again and in each experiment uterine contractions were promptly abolished only to recur after the pharmacological effect of Pitressin was expended. If the rabbit is given stilbestrol 1.0 mg. and progesterone 5.0 mg. daily for five days all the intrinsic motility of the uterus is lost; the uterus becomes totally refractive to both Pitocin and Pitressin (Fig. 6). Consider the contrast between the urethane-anesthetized rabbit and human uterus; progesterone sensitizes the human myometrium to Pitressin, while it renders the rabbit uterus insensitive to the hormone.

Hormones and the Guinea Pig Myometrium

The guinea pig uterus is under endocrine influences different from either the human or the rabbit. The guinea pig has regular cyclic ovulation (about eighteen days) during which time the uterus cyclically comes under the influence of estrogen. It has an intrinsic motility since it is the receptor organ for endocrine stimulation (Fig. 7).

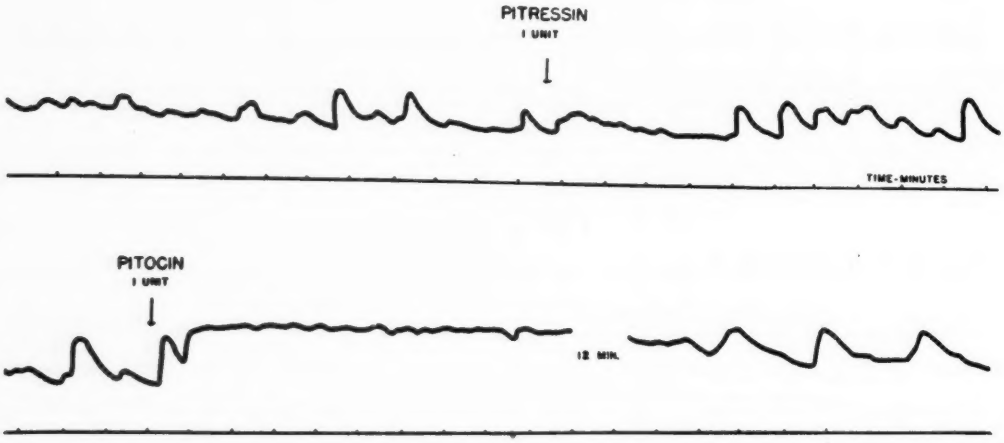

Fig. 7.—Guinea pig uterus untreated. Intrinsic motility shown. It is refractory to Pitressin and highly sensitive to Pitocin.

Effect of Estrogen and Progesterone.—The intact guinea pig uterus under urethane anesthesia reacts to estrogen and progesterone in a manner quite different from either the human or rabbit uterus. The untreated intact guinea pig uterus has an intrinsic motility which is more definite in pattern than that of the rabbit uterus and more closely approaches the preovulatory (estrogen) type of human myometrial contractions (Fig. 7). The contractions occur at a rate of about two per minute and have a duration of about twenty seconds which roughly parallels the human uterus, but stands in contrast to the rabbit uterus in which contractions are of very short duration, lasting barely more than ten seconds. When an estrogen (stilbestrol) is administered to the guinea pig in a dose of 0.5 mg. intramuscularly daily for seven days, all uterine motility is abolished, the uterus becomes passive, no contractions can be recorded (Fig. 8). If the guinea pig receives stilbestrol 0.5 mg. and progesterone 1.0 mg. daily for seven days, the uterus continues to remain noncontractile (Fig. 9). In its response to both estrogen and progesterone its reaction is entirely different from that of either the human being or the rabbit.

Effect of Pitocin and Pitressin.—The intact guinea pig uterus (urethane anesthesia 4 c.c. per kilogram of body weight, 25 per cent solution orally) is totally passive to Pitressin, but if the guinea pig be given Pitocin in a dose of 1 unit a prompt and sustained oxytocic response occurs. Commercially, Pitocin and Pitressin are checked for purity upon excised immature guinea pig uteri where Pitocin is strongly oxytocic and Pitressin is without effect. If the guinea pig now be given stilbestrol in a dose of 0.5 mg. intramuscularly daily for seven days all of its intrinsic motility is lost and it becomes refractive to both Pitocin and Pitressin. If the pig be given stilbestrol 0.5 mg. and progesterone 1.0 mg. intramuscularly daily for seven days, it is refractive to both Pitocin and Pitressin stimulation (Fig. 9).

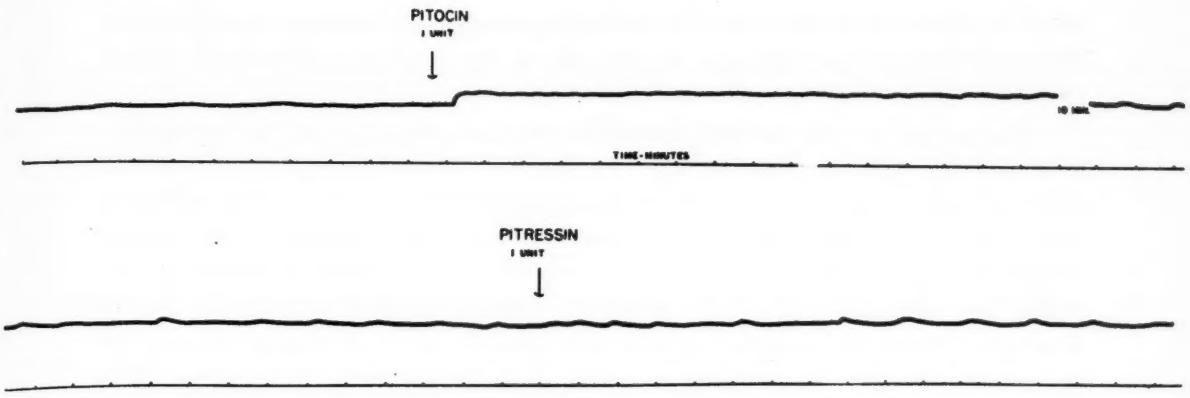

Fig. 8.—Guinea pig uterus stilbestrol treated. All motility abolished by estrogen. Refractory to Petressin and Pitocin.

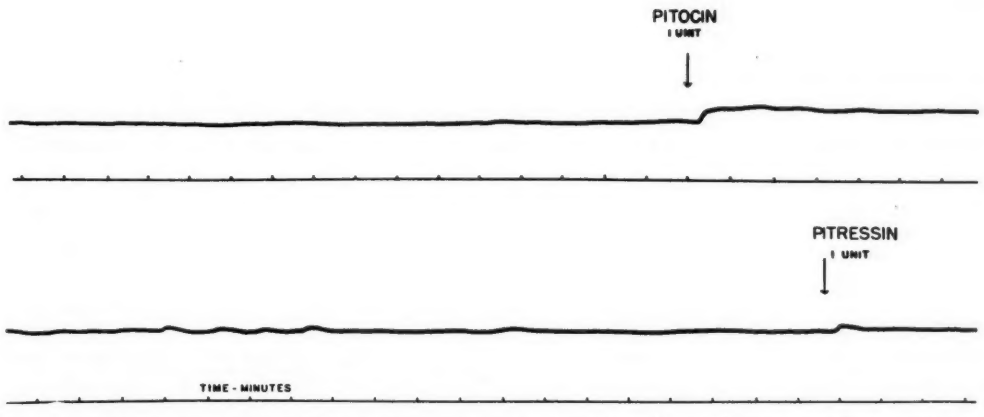

Fig. 9.—Guinea pig uterus stilbestrol-progesterone treated. All motility abolished. Slightly sensitive to Pitocin and refractory to Pitressin.

Discussion

A review of the observations reported above reveals that the human uterus is refractive to Pitocin in all stages of the menstrual cycle, but reacts in a highly irritable fashion to Pitressin during the postovulatory phase. The intact rabbit uterus untreated reacts to both Pitressin and Pitocin whereas the administration of stilbestrol to the rabbit greatly reduces the oxytocic effect of Pitocin and makes Pitressin an inhibitor of the myometrial contractions to the point where the uterine irritability is completely lost. The administration of progesterone to the rabbit makes the uterus refractive to both Pitressin and Pitocin. The untreated guinea pig uterus is highly irritable to Pitocin, refractive to Pitressin. Stilbestrol or progesterone or both render the guinea pig insensitive to Pitressin and Pitocin.

Observations made upon the effects of estrogen and progesterone on the rabbit or guinea pig uterus cannot be duplicated by similar experiments on the human uterus. Since so much clinical therapy is based upon conclusions of the laboratory, and since indeed the standardization and dose equivalents are often

based on such observations, the whole fabric of hormone therapy and standardization becomes subject to some question in so far as these observations are uncritically transferred to the human being.

The human uterus has been compared pharmacologically and physiologically to that of the rabbit and guinea pig. The human uterus during the reproductive years of life is under the cyclic estrogen-progesterone cycle of the maturing follicle and the corpus luteum, the rabbit uterus is under estrogen-progesterone influence only following coitus and/or experimentally induced ovulation, the guinea pig uterus is under cyclic estrogen reaching the peak during the periods of estrus. These are important physiologic variables which probably account for, but cannot explain the species uterine reaction differences to endocrines. Rendering the rabbit and guinea pig uterus "humanlike" in its endocrine environment by cyclic administration of estrogen and estrogen-progesterone still does not bring it to a comparable physiologic state with the human uterus.

The uteri from all three species have been studied in situ; the human uterus by means of an intrauterine balloon recording the myometrial contraction and the rabbit and guinea pig under urethane anesthesia by exposure of the uterus under a saline bath. This is an essential for comparative study. Isolating uterine muscle strips from their normal vascular and nerve supply so vitiates their response as to make comparative study even more impossible. Under near physiologic conditions, the reactions of these uteri to estrogen, progesterone, Pitocin, and Pitressin have been studied and the tracings are presented. The results obtained in the three species were in such wide variance that it may be assumed to be the result of species variations in endogenously produced hormones or intrinsic differences in uterine muscle physiology patterns. An attempt was made to induce in the rabbit and guinea pig an endocrine environment comparable to that of the human by the cyclic administration of estrogen and progesterone. Although the reaction patterns to Pitocin and Pitressin were changed in the rabbit uterus toward a reaction pattern in some respects simulating that of the human being, no such shift was observed in the guinea pig.

Conclusions

1. Patterns of uterine motility in the human menstrual cycle are well established. These are known to be related to estrogen production from the maturing follicle in the preovulatory phase of the cycle and to estrogen-progesterone from the corpus luteum in the postovulatory phase. The rabbit ovulates only upon coitus or artificial stimulation (pseudopregnancy) and has probably no intrinsic cyclic pattern of uterine motility. The guinea pig which has an estrus cycle of about eighteen days has an intrinsic cyclic pattern of motility.

2. The pattern of uterine motility in the human menstrual cycle can be reproduced in the human castrate by the cyclic administration of estrogen and progesterone, but nothing comparable to it can be induced in the rabbit or guinea pig by cyclic administration of estrogen and progesterone, at least

when measured under urethane anesthesia. Estrogen increases the irritability of the rabbit but not the guinea pig uterus; indeed, the administration of estrogen to the guinea pig renders the uterus noncontractile. Progesterone abolishes all uterine motility in the rabbit uterus and the guinea pig uterus. Estrogen increases the irritability of the human and rabbit uterus and depresses the guinea pig uterus. Progesterone increases the irritability of the human uterus and abolishes irritability in the rabbit and guinea pig uterus.

3. Pitocin is practically nonoxytocic to the human nongravid uterus both in the preovulatory and the postovulatory phase. Pitressin is strongly oxytocic to the human nongravid uterus in the postovulatory phase. The untreated rabbit uterus under urethane reacts to both Pitressin and Pitocin while the guinea pig uterus under urethane is totally passive to Pitressin, but highly irritable to Pitocin.

4. Assuming the results of laboratory experiment on the animal uterus in situ to be comparable to those of the human uterus has led to great confusion in endocrine therapy and the entire field must be critically reviewed. The development of rational endocrine therapy has been greatly retarded by the uncritical acceptance of animal experimentation. Physiologist, pharmacologist, and clinician should fuse their talents in the crucible of more intimate collaboration for the benefit of all.

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Medical Arts Building

Discussion

DR. RICHARD TORPIN, Augusta, Ga.—Dr. Bickers' emphasis that grave errors can result when data from animals are carried to the bedside without critical and careful interpretation is a well-directed observation. I am glad that he also has emphasized that estrogens and progesterone modify the threshold of the myometrium to stimuli and that these drugs should not be described as stimulative or inhibitory drugs. His results on Pitressin and Pitocin are to a large extent in agreement with those observed in human beings at the University of Georgia and the University of Tennessee. Our observations, however, do differ from those of Dr. Bickers in that we have found that the uterus will respond to Pitocin and Pitressin throughout the menstrual cycle. True, the threshold is markedly elevated during the first half of the cycle and the response to any given quantity of Pitocin and Pitressin is much smaller during the first half of the cycle. Yet the forty patients whom we have studied do show an increase in uterine activity following the intravenous administration of a small amount of Pitressin even during the first half of the cycle. In searching for an explanation for this disagreement of results, it would appear worth while to raise the question as to what quantity of fluid was placed in the balloons of Dr. Bickers' patients. In our patient 0.5 to 1.5 c.c. of fluid was placed in the balloons.

I present this slide to show the importance of the amount of fluid which is placed in the balloons. In this menstruating patient who had ovulated and whose estrogen levels were within normal range, it is possible to elicit two types of activity by placing different quantities of fluid in the balloon. Here the contractions are estrogenic in type. Here upon adding additional fluid, the progesterone type of activity results. It seems reasonable to suggest that the uterus of all patients potentially can respond by producing both of these types of activity and that the threshold of these two types of activity may be different.

The observation that estrogen and progesterone have totally different effects upon the myometrium of the human being, rabbit, and guinea pig is extremely interesting and important. I wish to call attention to the pronounced differences in dosages which Dr. Bickers used, i.e., with stilbestrol, estimating the body weight of the various animals: the daily dosages per kilogram of body weight were 80 mg. for the human being, 200 mg. for rabbits, and 1,250 mg. for guinea pigs.

Penttinen, Kari: On the Wassermann and Kahn Reactions During Pregnancy, Acta obst. et gynec. Scandinav. **27**: Supplement 3, 1946.

Penttinen, of Helsinki, in this 114-page monographic supplement reviews the serological studies on pregnant patients seen at the Maternity Center of the Women's Clinic during 1935 to 1945. In this interim, 20,145 pregnant women were seen and blood specimens were taken upon 18,090 cases (89.8 per cent). During the war years, 1941 and 1942, restrictions precluded serologic studies. In 451 cases (2.49 per cent), the Wassermann or Kahn reactions diverged from negative reports and in 393 instances full data were available. Among these series, 284 cases were regarded as "certain" cases of syphilis, 17 were "uncertain," and in 92 instances the positive syphilitic reaction was considered unrelated to syphilis.

Sixty per cent of the 284 syphilitic cases were in pregnant women aged 21 to 30 years and about 50 per cent of the group were primiparas and the other half multiparas. The positive results from cord blood of children were misleading in 28 per cent of the group.

Among the 92 false positive reactions, 70 were considered as due to technical errors (76 per cent). Pregnancy alone influencing false positive reaction was found only in fourteen cases. In all but two of the false positive reactions the positive results during pregnancy were weak, such as Wassermann, negative; and Kahn, plus one. The incidence of seropositive syphilis before the war (1935 to 1940) was 1.6 per cent, while during the war (1941 to 1944) the figure was 2.5 per cent. Wartime conditions increased the number of false positive results to 3 to 4 times as many as found under normal conditions. Thirty-three tables are included.

CLAIR E. FOLSOME.

SIMPLIFIED GYNECOLOGIC CARE*

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THE preparation of the gynecologic patient for operation twenty years ago was an awe-inspiring procedure. She was starved, dehydrated, and exhausted by repeated enemas until the "returns were clear." The perineum and abdomen were shaved and washed with soap and water the afternoon before. In addition, the abdomen was swabbed with alcohol and ether and covered with a sterile towel held in place by adhesive tape. Considerable effort was expended on douching, usually with a strong, antiseptic solution, in an attempt to eliminate bacteria from the vagina and perineum.

Operating room techniques were similar to those in use today, except that now we would call the caliber and quantity of suture material excessive. A double strand of chromic No. 2 catgut was the least to be used for the abdominal fascia. I have even seen chromic No. 4 catgut used by a master surgeon of the period. When silk was used, sometimes the braided strands were sufficiently strong to land a ten-pound trout! Moreover, the first assistant often would pull so tightly and enthusiastically on the continuous fascial suture, that he tended to lift the patient off the table. Stay sutures of wire or silkworm gut were commonplace and traditional, and no one thought a wound could remain intact without them. Any one of us, operated upon during that period, can remember how painfully they cut into the skin about the tenth day.

Postoperatively, the regimen was even more elaborate. Three-inch widths of overlapping adhesive tape nearly encircled the body from symphysis to xyphoid, prevented adequate chest expansion and held in place literally yards of gauze dressing. As if this were insufficient, a scultetus bandage constricted the abdomen and limited respiratory movement. If there was associated vaginal plastic operation, and multiple procedures were fashionable, a "T" binder held quantities of dressings over the perineum.

Upon return from the operating room the patient was received into an "ether" bed precisely made with flannel blankets and warmed by hot water bottles. Although the purpose was prevention of pneumonia, in effect, profuse sweating aided and abetted dehydration begun the day before. She was placed in Fowler's position with resulting interference of venous flow at the popliteal space. Small wonder that upon regaining consciousness she believed implicitly in her complete incapacitation and did not dare to move! Who among us, operated upon during that time, had the courage to overthrow these psychologic and physical restraints, and move around in bed?

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

The patient received no food and little fluid the first day. Sometimes crushed ice by mouth was allowed if she promised not to swallow. Water to drink was sheer poison, and intravenous infusions were uncommon. Occasionally, saline was administered by hypodermoclysis under the breasts, or in the thighs. Some clinics utilized the retention enema and gave a liter of water by rectum before the patient regained consciousness. Liquid diet might be permitted after the first twenty-four hours, but the laparotomized patient did not enjoy the privilege of a decent meal for days to come. Transfusion was invoked only upon dire necessity.

The abdominal wound was inspected frequently, but always with elaborate antibacterial techniques, including the use of sterile gloves. After careful removal of the dressings, the wound was surrounded by sterile towels and invariably swabbed with an antiseptic, before and after each manipulation. Skin clips or sutures were seldom removed before lapse of a week and silkworm-gut retention sutures remained until the twelfth or fourteenth day. The typical "railroad track" cross scars where retention sutures cut into the skin by reason of local ischemia are, alas, only too well known.

Exercise of an excretory function necessitated removal of the "T" binder and perineal dressings. Before resealing, bichloride, or other equally potent solution was poured over the perineum to re-establish the mental equanimity of nursing and medical personnel. With voiding and defecation so complicated, is there any wonder patients tended to "hold out" as long as possible? Such elaborate rituals undoubtedly inhibited the postoperative patient and increased the necessity for enemas and catheterization.

The care of the urinary bladder was a chapter in itself. Catheterization, multiple washings, frequent instillation of antiseptic and determination of the amount of residual urine were performed in utter disregard of the fact that the bladder wall muscularis and mucosa usually remained intact throughout the course of the operation. Such meddlesome interference inevitably resulted in a number of bladder infections, and not infrequently in severe cystitis. I remember a case of hemorrhagic cystitis where the mucosa of the bladder sloughed out through the urethra and the patient succumbed as a result.

Such was the pre- and postoperative care on a typical gynecologic service of twenty years ago.

Beginnings of Simplification

Modification of such a vigorous regimen was inevitable, and by the early 1930's a few courageous souls began to doubt the necessity of some aspects of these pre- and postoperative rituals. It was realized that gynecologic surgical attack seldom involved the intestines and that starvation was, therefore, unnecessary. Similarly, it was learned that a single enema sufficed to empty the rectosigmoid. The realization of the necessity to maintain fluid balance, both pre- and postoperatively, was undoubtedly speeded by the piteous begging of the immediately postoperative patient for water to drink. Consequently, by the middle of the fourth decade of this century, patients were allowed to eat and drink normally up to bed time of the evening before.

Also, the care of the abdominal wound was considerably simplified. In general, the trend was toward reduction of the caliber and quantity of suture material. From a personal standpoint, the biggest single step toward simplification of wound care, and requiring great courage, was elimination of stay sutures. Once this hurdle was surmounted, and the break with tradition consummated, the rest of many simplifications followed easily. Nevertheless, many a long day passed, and numerous patients were operated upon without subsequent dehiscence before we believed in actuality the doctrines we were preaching. Sutures were removed earlier following the observation that if left too long they cut into the skin and produced stitch abscesses. Fewer dressings were placed over the abdominal wound. Above everything else we learned to avoid compression of the lower ribs with adhesive tape and thus permitted free and easy expansion of the chest. Moreover, we tended to remove bandages at an earlier period than before and ultimately to use only a few pieces of gauze over the wound.

Perineal care was greatly simplified according to the ideas laid down by Plass,[1] and originating in 1916 with his article, "Post-Partum Care of the Perineum." Plass was able to show that "scientific neglect" gave at least as good, and perhaps better, healing than more elaborate means. Consequently, no perineal dressings, "T" binders, or pitcher douches were ever employed on any gynecologic service of my association. Even with vaginal hysterectomy, anterior, and posterior colporrhaphy, no attempt was made to achieve or maintain perineal antisepsis. Postoperatively, the region was washed with soap and water, using a clean, but not sterile, washrag, and dried with a towel.

We began to feed patients soon after operation in the belief that early resumption of normal intestinal flow tended to prevent paralytic ileus. There was some scientific basis for this, learned during efforts to make intravenous pyelograms on rabbits. The enormous colon of these animals necessitated minimizing fecal material and gas in order to obtain satisfactory films. Cathartics, enemas, starvation, and conversely extra feeding, were employed in efforts to eliminate as much gas as possible. Of all the methods, starvation produced maximal amounts of gas, since it slowed the fecal stream and encouraged growth of putrefactive bacteria. Postoperatively, intravenous fluids came into general use and sometimes the patient was allowed to drink water by mouth.

From the standpoint of prophylaxis of venous thrombosis two positive measures, and one negative, were employed. In some instances, patients were given desiccated thyroid days before operation in an effort to speed up the metabolism and the heart rate. They were encouraged to move in bed immediately postoperatively and positive orders to insure turning from side to side every few hours were issued. It finally became evident that Fowler's position, once so popular among gynecologists, encouraged stasis of blood in the popliteal space. The position is seldom employed today.

During this period of simplification of care, there came into the hospital a thin and frail 74-year-old woman with a cystic ovarian mass at least the size of a term pregnancy. She seemed to be a most promising candidate for postoperative pneumonia, at a day and time when modern "miracle" drugs were unavailable. It was obviously desirable to at-

tempt operation because of respiratory embarrassment. The tumor was successfully removed, and, with trepidation lest the wound break wide open, we lifted the patient upright into a chair the afternoon of the day of operation. By the third or fourth day she was walking to the bathroom. If a 74-year-old woman could tolerate early rising from bed why not young women also?

We learned to avoid brachial palsies when the patient was in Trendelenburg's position by removing the shoulder brace on the side of the abducted arm. A pillow under the small of the back during deep anesthesia tended to prevent loss of the lumbar curve and low back pain. Also, backaches resulting from undue flexion of the thigh upon the trunk and of the leg upon the thigh, were avoided by raising the leg holders over and above the protests of the operative assistants wishing to view the steps of a vaginal operation.

Most of these lessons were learned the "hard way," by all surgeons of the period, and no one man was responsible for the introduction of a number of them.

Development of Simplification

The third period in my life as a gynecologic surgeon began with assumption of the directorship of a hospital service. Policies of simplification, begun elsewhere, were continued and expanded. One of the first problems to be attacked involved the amount of preliminary vaginal preparation necessary for total abdominal hysterectomy. Obviously, the way to ascertain the minimum necessary preparation was gradually to reduce to nothing. Following a series of total hysterectomies performed without previous vaginal preparation except catheterization of the urinary bladder, we found a decided increase in postoperative morbidity. Apparently, the vagina must, at least, be cleansed. Today, therefore, it is washed in the operating room with green soap and water, and dried with a sterile sponge. The term "washing" is used advisably, since the vagina is washed and not scrubbed. The urinary bladder is emptied by catheterization.

Although every effort is made to bring the patient to the operating room with proper hemoglobin and red-blood-cell values, there is sometimes unusual blood loss during the course of operation. In consequence, many laparotomized patients were transfused during the course of operation. Ultimately, the inevitable happened and an incorrectly matched blood transfusion was given to an anesthetized patient, with resulting lower nephron nephrosis. Following this unfortunate accident, we administer no transfusions to unconscious patients, except in dire emergency, since they are unable to report the beginning symptoms of incompatibility. This can hardly be classified as a step toward simplification of care, but is included for the sake of completeness.

Gradually, we learned to achieve mental equanimity regarding maintenance of postoperative fluid balance. After administration of fluids by the intravenous route became commonplace, it was inevitable that the pendulum should swing too far, and many patients suffered from overload of the vascular bed. In this instance, the doctrine of "where a little is good, more is better" does not hold true. Today, we limit the daily intravenous administration of fluid to the postoperative patient to 2,500 c.c. of isotonic solution. On the day of operation, this amount is supplemented by transfusion of quantities of blood equivalent to that

lost. Since the adoption of this policy, there has been no case of postoperative pulmonary edema.

In line with general experience throughout the world, early ambulation proved to be the best answer to the question of prophylaxis of venous thrombosis. Postoperative patients of all types are allowed up when fully conscious. We have followed this principle for more than five years. Many patients do not understand the idea of early ambulation. It should be explained to them that it is important, as soon as possible after operation, to stand or sit erect with the feet hanging down. Moreover, they must understand that early return to the erect posture does not mean forcible and permanent ejection from bed. Most patients accept the principle of early ambulation as soon as they understand that they may spend the majority of their time in bed, arising daily, but only on occasion.

As a by-product of early ambulation, the necessity for elaborate care of the urinary bladder decreased. The inability of the gynecologic patient to void stemmed from long years of inhibitory training rather than as any result of operative attack on the bladder. Because there is little need for bedpans when patients are permitted to get up at will, there is also little need for catheterization for distress. The bladder does not become overdistended, and the amount of residual urine is relatively unimportant. Actually, there are only a few gynecologic procedures where it is necessary to maintain postoperative bladder collapse. These include the Wertheim operation, vesicovaginal fistula repair, and radium application, during the time radium remains in place. We abandoned catheterization for residual urine following anterior colporrhaphy and, in fact, all other operations except the ones mentioned above. In essence, we have virtually discarded the use of the catheter and of catheterization on the gynecologic service. I might interject that this also holds true on the obstetric branch of our service.

Care of the Wound

The most radical departure from established custom lies in our care of abdominal wounds. *Ultimately, we learned that it was impossible to manufacture a new abdominal wall with adhesive tape and sutures.* Natural processes will heal the wound firmly and strongly, provided we approximate it anatomically and accurately without constriction and with the minimum amount of suture material. Stitches in the anterior rectus fascia and throughout the closure are tied so loosely that it is possible to insert a clamp under them. Earlier, the reduction of the quantity and the duration of maintenance of dressings were mentioned. Three years ago we realized the quantity of dressings was minimal. Moreover, they were removed several days later when the skin clips were removed. On Jan. 1, 1946, we adopted the policy of employing absolutely no dressing on any abdominal wound. There are a number of theoretical advantages to the practice. First, the wound is allowed to seal itself with fibrin within a few minutes after suture. Second, the fibrin seal is a far more effective protection against bacterial invasion than gauze. Third, the moisture otherwise accumulating underneath any dressing evaporates and does not liquefy the

fibrin seal. In practice, as soon as the wound is closed it is left strictly alone. No antiseptic of any nature is put on it either in the operating room or later during the postoperative healing course.

This treatment of wounds is not such a new departure, because the policy is employed by almost all plastic surgeons and was used in gynecology years ago by Berkeley and Bonney. In their *Textbook of Gynecologic Surgery*,[2] they state, on page 25, "At the Middlesex Hospital we gave up all dressings for clean wounds twenty-seven years ago. A sterile towel is placed over the wound in the theatre and maintained there until the patient has recovered consciousness."

Table I shows our experience with uncovered abdominal wounds during the past three years, as contrasted with the experience of the two previous years when wounds were dressed, albeit with a minimum of gauze. It is readily seen there is virtually no difference between the two series, so far as incidence of complications is concerned. In order to test the matter still further, 100 consecutive patients submitted to laparotomy during the latter half of 1947 were studied with half of the wound dressed and the other half uncovered. The series was equalized by alternating dressing of the upper and lower half. Table II shows the result of this study. A standard sterile dressing for one-half of the wound consisted of six gauze squares, 4 by 4 inches. Skin clips closed all wounds and no retention sutures were employed. The dressing over half the wound and the skin clips were removed on the fourth postoperative day. Bacterial cultures in tryptose broth were taken both from the open and the dressed portion of the wound. The patient's reaction to the lack of dressing was recorded on the fourth day.

TABLE I. WOUND HEALING

	TYPE OF DRESSING	
	CONVENTIONAL (JAN. 1, 1944, TO DEC. 31, 1945)	NONE (JAN. 1, 1946, TO OCT. 31, 1948)
Patients, number	203	258*
Superficial separation	4	4
Infection	8	10
Dehiscence	1	1

*In addition, 100 patients were submitted to comparative study.

TABLE II. COMPARATIVE STUDY OF 100 WOUNDS; ONLY HALF OF WOUND DRESSED

	DRESSED PORTION	OPEN PORTION
Infection, severe	4	0
Infection, slight	7	5
Slight serosanguineous exudate	3	0
Slight wound-edge separation	8	1
Granulating at 6 weeks	5	2

In general, the number of colonies of bacteria from both the dressed and open portions were similar. However, it was noteworthy that there tended to be more pathogenic bacteria underneath the dressing than on the open portion. On the open portion the organisms were more nearly of the type commonly found on skin surfaces anywhere.

Patients' opinions on the comfort of the wound were interesting. Thirty-six patients preferred no dressing, twenty-six preferred a dressing, and thirty-eight had no preference. Of the complaints, the most common included: "the skin clips catch on the bed clothes," "afraid to look at wound," "afraid wound will fall apart." Some of the comments of the examiner made at the time the dressing was removed were as follows: Covered portion of the wound, "increased

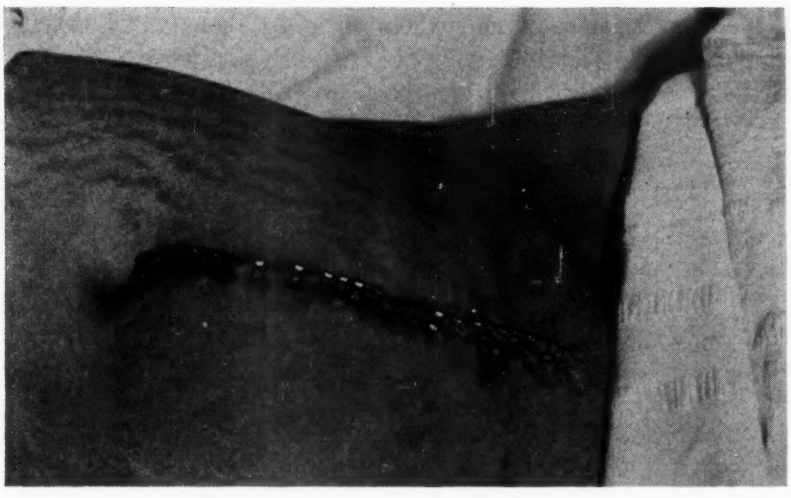

Fig. 1.—Appearance of wound twenty-four hours after operation for ruptured tubal pregnancy.

Fig. 2.—Same patient as in Fig. 1. Appearance of the wound on the third postoperative day shorty after removal of clips.

serum," "more tender," "moist, reddened, macerated, bleeds easily when dressing is removed." Open portion of the wound, "better agglutination," "stronger fibrin seal," "skin clips a little bit more difficult to remove because of the small amount of clotted blood around them." Figs. 1, 2, and 3 represent photographs made twenty-four hours after operation, on the third day, and one month later.

In essence, this story of the simplification of pre- and postoperative care parallels the period of my development as a gynecologic surgeon. As such, there is little of newness, since most of you underwent identical experiences. It was inevitable that, following the birth of modern surgery, techniques should be cumbersome and complicated, since with lack of knowledge and experience we tend to overcompensate. It is also obvious that some of our modern techniques are essential, and others persist through custom. Therefore, it is desirable to invoke a quizzical attitude, question our techniques, and constantly look for simpler methods.

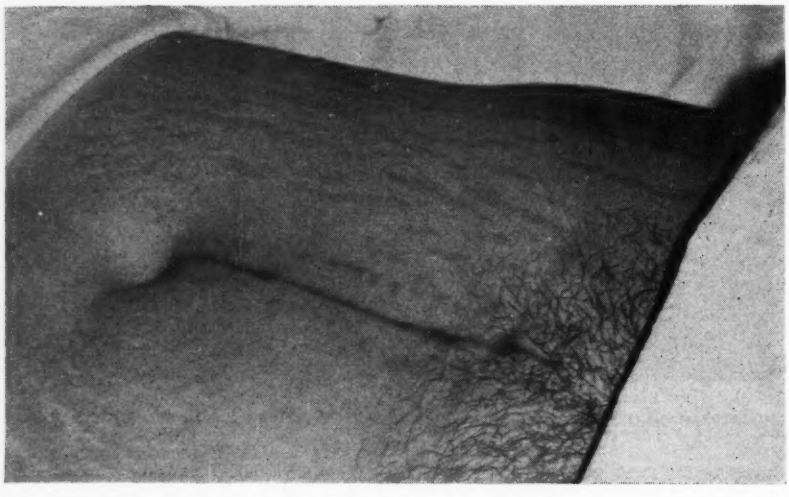

Fig. 3.—Same patient as in Fig. 1. Appearance of wound thirty days after operation.

Perhaps we have become too radical in our simplification at Parkland Hospital, especially in the care of abdominal wounds. It would be foolish to claim that leaving abdominal wounds uncovered results in greatly improved healing. Such is not the case, since the numerical differences in our two series are not sufficient to be statistically significant. On the other hand, it would seem to be permissible, from the evidence presented, to make the statement that employment of any type of antiseptic or dressing on clean, abdominal wounds is entirely unnecessary, except for the sake of adherence to time-honored custom.

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LATE LIGATION OF THE UMBILICAL CORD*

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TEN years ago I presented to this Association the work of Dr. Frischkorn and myself[1] on the effect of severing the cord at varying lengths of time. We were interested in the amount of blood left in the placental vessels and the effect of this upon the red blood cell count of the infants. In 400 unselected infants delivered under Sodium Amytal, scopolamine, and ether anesthesia, the cords were clamped and cut at varying time intervals from one to fifty minutes. There was scarcely any correlation between the length of time elapsing before the cord was clamped and severed, and the infant's red blood cell count. The coefficient of correlation as figured by the Pearson formula was $+0.105$ and the probable error ± 0.0329. The coefficient between the time of ligating the cord and the amount of blood left in the placental vessels was $+0.2564$ and the probable error ± 0.0315. Since the coefficient is more than six times the probable error it is considered significant, although it is small. There was, as would be expected, a more significant negative correlation between the fetal red blood cell count and the amount of blood remaining in the umbilical and placental blood vessels. The coefficient of this correlation was -0.36 which is more than twelve times the probable error of ± 0.0293. We found that whether or not the cord had ceased to pulsate was the significant factor and not the length of time that the exposed cord was allowed to pulsate. The average red blood cell count of the babies whose cords were allowed to cease pulsating before being cut was 584,481 greater than that of the babies whose cords were cut at once. We were also able to confirm the early observations of Schückling[2] and Haselhorst[3] that the baby gained approximately 100 grams in weight when the cord ceased to pulsate.

We were not impressed that the increased red blood count of one-half million made any noticeable difference to the average baby while he was in the nursery, but thought that it might make a significant difference to a premature or weak baby. We were also impressed that, in our series, the cords continued to pulsate for a longer time than in Budin's[4] cases, and we thought that this difference might have been due to the anesthesia that our patients received.

Since our paper was published, Windle[5] has noted that the infants with late ligation of the cord had 6,010,000 red blood cells and 22.1 Gm. of hemoglobin and the babies whose cords were ligated immediately, 5,450,000 and 19.5 Gm. of hemoglobin, and that this difference continued for at least the first week of life. Ballentine[6] has stated that the advantage of late ligation of the cord persisted until the baby left the hospital. Recently, Evans,[7] in discussing surgery in the newborn, stressed the advantage of this "auto transfusion" which the baby received when the ligation of the cord is delayed.

*Read at the annual meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949.

Recently I had a check made on babies just before they were discharged, from the fourth to the seventh day. The red blood cells of 73 babies whose cords were ligated after pulsation in the umbilical arteries had ceased averaged 5,938,000 in comparison with an average of 5,657,000 of 68 babies with early ligation. The percentage of hemoglobin in the first group averaged 119.5 in comparison with 115.7 of the second group. The anesthesia of the mothers was usually vinbarbital-hyoscine and intravenous Pentothal Sodium. Since we had also changed the technique of the third stage of labor it was thought worth while to repeat our former observations.

The management of the third stage of labor is that recommended by M. E. Davis[8]: as soon as the anterior shoulder appears the mother is given an ampule of Ergotrate intravenously. The cord is cut between clamps as close to the vulva as convenient so as to leave as long a section of cord attached to the baby as possible. The placenta is delivered by the Brandt method as described by Andrews.[9] In fifty cases, selected at random, the cords were not clamped nor tied, and the placentas were delivered by Credé's method, the baby was placed in a warm bassinet and the cord was divided only after all pulsation had ceased.

It was evident that with the intravenous Ergotrate the cords ceased to pulsate sooner. In Dr. Frischkorn's and my series one cord continued to pulsate for fifty minutes and many pulsated for thirty or forty minutes. In the present series many cords had ceased pulsating before the placenta was delivered, a matter of three to four minutes. Only two continued to pulsate as long as twenty minutes, the longest interval being twenty-three minutes. As noted in the previous paper the cessation of pulsations in the umbilical vessels begins at the placenta and proceeds toward the umbilicus and when this occurs the vessels collapse. The vessels on the fetal surface of the placenta are then no longer congested.

TABLE I. RED BLOOD CELL COUNTS IN CASES OF EARLY AND LATE LIGATION OF THE UMBILICAL CORD

	EARLY LIGATION	LATE LIGATION	DIFFERENCE
No Ergotrate (333 cases)	5,198,919	(59 cases) 5,783,400	584,481
Intravenous Ergotrate, count on discharge (68 cases)	5,657,000	(73 cases) 5,938,000	281,000
Intravenous Ergotrate, count on first day (50 cases)	5,740,000	(50 cases) 5,870,000	130,000

In fifty cases in which there was early ligation of the cord the red blood cell counts of the infants varied from 4,650,000 to 6,840,000, the average being 5,740,000. The hemoglobin varied from 98 per cent to 125 per cent. The average was 113 per cent. The hemoglobin determinations were done by the micro method and 125 per cent is the highest reading on the machine. Three times the reading was reported as 125 per cent plus. Hence the average of 113 per cent is a slight understatement. In fifty cases in which the ligation of the cord was delayed until after the umbilical vessels had ceased pulsating, the red blood counts varied from 4,710,000 to 6,920,000 with an average of 5,870,000. The

hemoglobin varied from 107 per cent to 125 per cent plus. In this series there were seven cases reported as 125 per cent plus. The average, making no allowance for the plus signs, was 116.4 per cent. The difference in the two averages of fetal red blood cells is only 130,000. This is even smaller than the difference of 280,000 which I found between early and late ligation of the cord, when the blood counts were made just before the baby left the nursery. The difference is so small as hardly to justify the more difficult technique of delivering the placenta before severing the cord.

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(The paper, "An Evaluation of the Radical Hysterectomy in the Treatment of Carcinoma of the Cervix," by Drs. James F. Donnelly and Jesse B. Caldwell, Winston-Salem, N. C., which was also read at the Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Williamsburg, Va., Feb. 10 to 12, 1949, will be published in the January issue.)

Donahue, W. L., and Fremes, I. A.: Maternal Isoimmunization Without Evidence of Clinical Erythroblastosis Fetalis in the Newborn, J. Lab. & Clin. Med. **33**: 526, May, 1948.

The authors introduce their study with a discussion of the subsequent obstetrical course of women who have delivered an erythroblastotic infant and a brief review of reported cases similar to their own.

Two well-documented cases are then presented in which normal infants were delivered of isoimmunized mothers who had previously borne erythroblastotic infants. These normal infants, furthermore, possessed the proper Rh pattern for the development of this disorder in each instance. The roles of the placental barrier and Rh genetic subdivision are discussed. S. B. Gusberg.

Scott, J. A., and Benjamin, B.: Weight Changes in Pregnancy, The Lancet, page 550, April 10, 1948.

Monthly rates of weight gain were calculated from the records of 1,014 pregnant women on the British wartime diet supplemented by extra rations. Maximal gains occurred in the fifth (4.24 pounds) and sixth (4.70 pounds) lunar months. Thereafter, the rate gradually fell to 2.55 pounds in the last month. In this month 150 women (14.8 per cent) gained nothing. The average total weight gain was 22 pounds. Irving L. Frank.

American Gynecological Society

Transactions of the Seventy-Second Annual Meeting, May 16 to 18, 1949, at Hot Springs, Virginia.

(Continued from the November issue)

TRENDS IN THE USE OF THE CESAREAN SECTION OPERATION*

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IN THE course of studying a series of cesarean sections performed at the Sloane Hospital during the past six years it was apparent that some interesting trends in the scope of the operation were taking place. For this reason it seemed that it might be of value to determine the nature of these trends over a longer period of time, more especially in relation to the changing attitudes toward the indications for the operation. The present survey therefore starts in 1934 and includes 1948, so that fifteen years of experience are reported.

Gross Trend

Of interest, first, is the over-all trend for the total use of the operation. In Fig. 1, the cesarean section incidence for the larger obstetrical services in Manhattan is shown. The curve representing the total incidence of the combined services of Woman's Hospital, Sloane Hospital, New York Hospital, and Bellevue, for the years 1934 to 1948 inclusive, shows that after a fairly steady incidence just below 4 per cent up to the year 1941, there has been a definite tendency for an increased rate since that time. This combined rate has presently reached 6.2 per cent. The upward shift dates to the introduction of antibacterial therapy, which, more than any other factor, has definitely widened the scope of the operation. The inauguration of hospital blood banks came at about the same time and these, no doubt, have also played a role in this upward trend.

If the services are considered individually, the same tendency for an increasing rate since 1942 is noted in each of them but to a variable degree and from a different base. The Bellevue Service is somewhat of an exception in that the rising incidence which began there in 1944 has again returned to pre-antibiotic levels in the last two years. The New York Hospital and our own service continue to show an upward trend. At the Woman's Hospital, where the higher rate for abdominal delivery began before that of the others, a top figure was reached two years ago and their rate now seems to be leveling.

*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

Assuming that a patient will return to the institution that performed the primary section, it is obvious that any broadening of the indications will result in an even greater increase in the total operations due to the repeat sections. This no doubt partially accounts for the present high rate at Woman's Hospital and will be a factor in the rates of the other hospitals during the next few years, even if there is no further change in their cesarean policies.

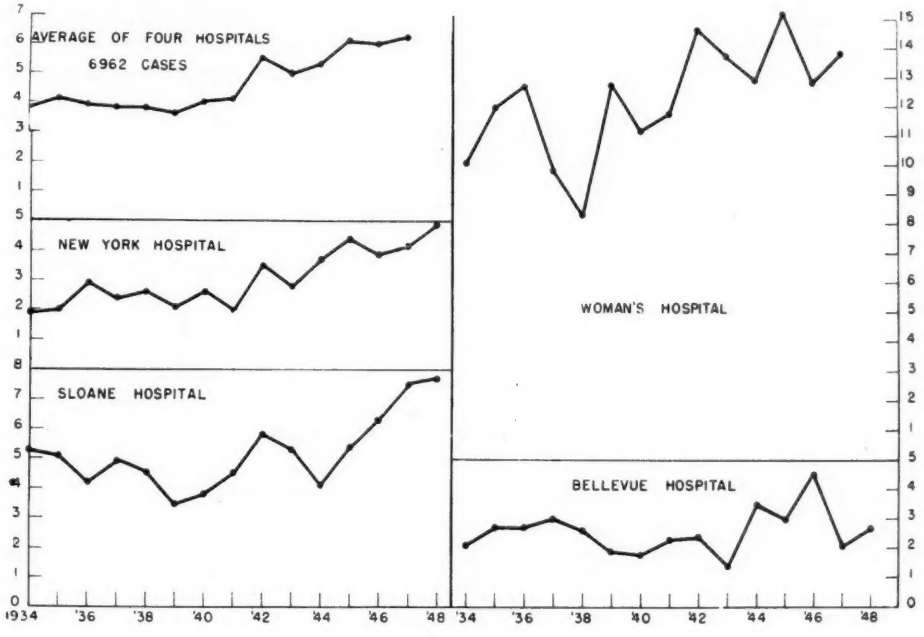

Fig. 1.

Vaginal vs. Abdominal Operations

Another trend that deserves mention deals with the extent to which the cesarean section is replacing other vaginal operations.

In Fig. 2, operative deliveries are calculated as the total number of cesarean sections, midforceps, high forceps, breech extractions, versions—except those done for the second twin—and craniotomies. It will be noted first that there has been no increase in the total incidence of these operative deliveries. If anything, there has been a slight decrease. When the cesarean sections are calculated as a percentage of these total operative deliveries it is observed that for the past ten years there has been a slow but steady substitution of the abdominal delivery for the other obstetric operations in such a manner that, while in 1939 the cesarean sections constituted 35 per cent of the total operative deliveries, in 1948 they rose to exactly 70 per cent. Since, as already pointed out, there has been no material change in the total number of obstetric operative procedures, it follows that the cesarean section has been replacing the other operations. This substitution has been made with an extremely low maternal loss. We have performed the last 1,064 consecutive cesarean sections without a single maternal death.

It is of interest to consider for a moment the possible shape of this curve in the next ten years. If 70 per cent of the major operative deliveries are now done by the abdominal route, is it probable that at some future time

nearly all the more difficult operative deliveries will be done in this way? Is it likely that we may reach a point when vaginal procedures that require operative force will be performed only on the rarest occasions? The trend seems to be very much in that direction and unless some unforeseen factors introduce a discontinuity of the curve, we shall be practicing that kind of obstetrics within the next ten years.

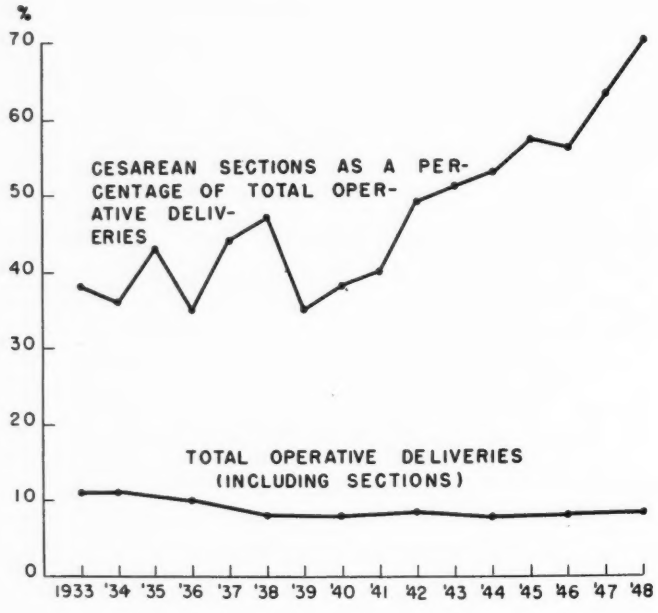

Fig. 2.

In view of these changes we should ask ourselves how they might affect the practice of obstetrics. At first thought, realizing that this eliminates much of the operative surgery of the labor room, which after all has been the stock in trade of the experienced obstetrician, it might suggest that the specialty will gradually revert to a sort of expert midwifery garnished by the cesarean operation. Let us develop this idea a little farther. The management of labor by either easy vaginal delivery on the one hand or cesarean section on the other could be achieved by adopting one of three polices. The first would aim at very broad indications for the cesarean section operation in such a manner that the operation would be done at the slightest departure from normal labor. This policy can never gain favor because there will always be an advantage in the normal delivery. The factors which make the cesarean section operation so safe today make the normal vaginal delivery even safer. Greater safety, especially to the mother, will always be inherent in the normal delivery and for that reason we will never reach a stage in the development of the specialty when the cesarean section rate may be permitted to rise with impunity. A second policy, in some ways the reverse of the first, might readily favor the operation in such obvious complications as placenta previa, but would allow long trial labors before abdominal section was done for the dystocia problems which, of course, constitute the majority of the indications. Such a policy would undoubtedly result in a desirably low section rate and, presumably, a low vaginal operative rate if desistance from vaginal operations could be practiced until a full second stage had been given. If we reach a

point that permits this kind of obstetrics with safety to mother and child, we may well have the substitution of a team consisting of general practitioners and general surgeons to manage labor instead of the obstetrician. This policy may be seemingly quite practicable in view of the protection from infection afforded by the antibiotics and modern supportive therapy, and would have far-reaching effects in changing the present pattern of obstetrics as a specialty. In many quarters this policy is actually followed today but it has definite drawbacks which will keep it from gaining favor. Apart from the many prolonged and needless trial labors, it has the same deterrent argument against it that was made for the cesarean *ad lib.* policy, namely, that if these late cesarean sections can be made safe, earlier sections will be even safer to the mother and more so to the child.

A third policy, and what seems the most acceptable, would emphasize the need for better methods of prognosticating the pattern and end result of labor based on pelvic and fetal anatomical relationships and the potentialities of the contracting uterus. The obstetrician's chief interest would lie more with the problems that confront him at the begining of labor rather than with its end. This naturally puts the emphasis more on an understanding of the physiology of labor than on obstetric surgery. With this change of viewpoint, he should develop increasingly precise tools that will enable him to determine with a high degree of accuracy the cases that will have dystocia and those that will deliver easily by their own efforts. In this way he will eliminate a great deal of vaginal obstetric surgery and still maintain a low cesarean section rate. But even before all this may be possible, the obstetrician will gradually reduce the incidence of vaginal operative deliveries by accepting a less rigid definition of cephalopelvic disproportion based on his present prognostic methods and by simply substituting the cesarean section for difficult vaginal deliveries when the occasion for such deliveries unpredictably arise.

Disproportion

Cephalopelvic disproportion is the indication for cesarean section that is most difficult to define especially when relative degrees are considered. In order to determine the changing percentage of cases of cephalopelvic disproportion treated by cesarean section, the total number of these cases should be known—those that are sectioned, the ones that are delivered operatively per vaginam, and the group that overcome the disproportion by moulding after vigorous labor finally to deliver normally. Since this total group is not available as such from the files and for want of a more satisfactory basis of calculation, it would seem best, although not ideal, to express the changing incidence of cesarean section for disproportion as a percentage of primary sections for this indication among the total primiparas delivered. In Fig. 3 it will be noted that up to 1942 about 2 or 3 per cent of our primiparas were sectioned for disproportion. Since that time the policy in this respect has fluctuated, but within the last three years there has been a steady rise so that, in the last year, 5.8 per cent of the primiparas were so managed. Some error may be present in these figures due to the fact that the Negro group has increased from 20 per cent at the beginning of the study to 38 per cent in more recent years. While this change in the racial cross section of the cases may of itself account for part of the increase in primary sections for disproportion, it is believed that the increase is due primarily to a broadening of the policy of performing the operation in cases of relative disproportion.

Perhaps the best data to substantiate the value of such a policy is noted in the fact that cranial birth injuries, as revealed by our autopsy files, have been reduced to very nearly one per thousand births. The maternal outlook has

also improved. In the first half of this study there were two maternal deaths among the 138 primary sections done for cephalopelvic disproportion, and in the last half there have been no maternal deaths in the 214 sections performed for this reason.

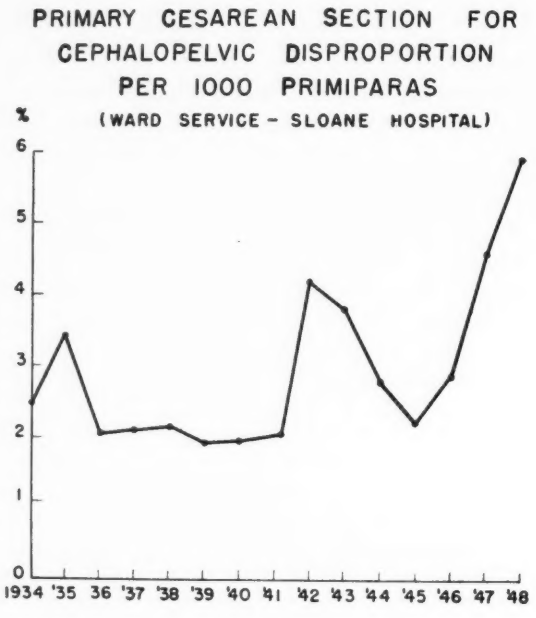

Fig. 3.

Uterine Inertia

Frequently associated with cephalopelvic disproportion is the condition of uterine inertia. A division of these cases into three five-year periods (Table I) shows no change in the incidence of the operation with a small reduction in fetal mortality. Since it was our clinical impression that an increasing number of sections are done in this category, it is likely that the discrepancy between the figures and this impression is due to the fact that those cases of uterine inertia associated with abnormal pelvis are listed under cephalopelvic disproportion as the primary indication and therefore do not appear under this category. The two indications are not always separable.

Pituitrin infusions, which are currently employed for this condition, have not been used long enough to have had any appreciable effect on the figures, but it is likely, judging from our limited but favorable experience, that this condition, when it is not complicated by other factors, will require cesarean section less often in the future.

TABLE I. CESAREAN SECTION IN UTERINE INERTIA

	CASES	CESAREAN SECTION*	CORRECTED FETAL MORTALITY
1934-1938	292	5.1%	5.5%
1939-1943	280	6.4%	3.6%
1944-1948	224	5.3%	4.0%

*Uterine inertia was *primary* indication.

Placenta Previa

The trend in the use of the cesarean section for the management of placenta previa indicates that this operation is being used more frequently all the time and is without any doubt the method of choice (Fig. 4). The figures indicate that it is now used in 75 per cent of the cases, where it seems to be leveling off. The one case of placenta previa out of four that is delivered vaginally is generally managed by simple measures, such as rupture of the membranes followed by spontaneous delivery. The vaginal deliveries also represent minimal degrees of the condition, with only a small amount of bleeding. Here, more than in any complication in obstetrics, we have reached the simple formula which may be expressed as: vaginal delivery without interference or cesarean section. It is not inconceivable that there will be a growing tendency to deliver all cases of placenta previa by cesarean section. One point of argument for such a policy could be based on the fetal mortality rate.

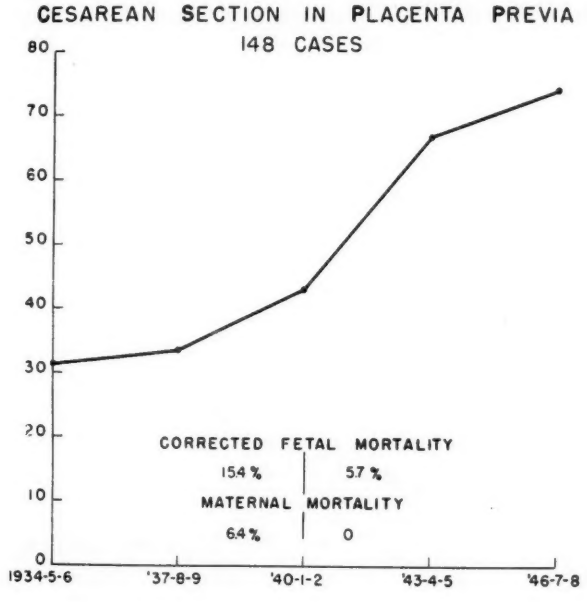

Fig. 4.

In the first half of this study this rate averaged 15.4 per cent when corrected for the congenitally malformed fetuses, antepartum intrauterine deaths, and babies that weighed less than 2,000 grams. The cesarean section incidence for this condition then averaged 30 per cent. In more recent years the fetal mortality rate corrected in the same way has dropped to 5.7 per cent. It could be argued that the fetal death rate can go still lower by treating placenta previa unequivocally by cesarean section.

Of further interest is the fact that the maternal death rate for the first half of the series was 6.4 per cent and that the six fatal cases, making up this group, were all delivered vaginally by some operative means or another. In the past nine years, following what seems to be a more conservative policy of doing either a cesarean section or uncomplicated vaginal delivery, the maternal mortality has been zero. In the past fifteen years we have not lost a single mother with placenta previa who was delivered by abdominal section.

Breech Presentation

As in many of the other indications for cesarean section there has been an appreciable increase in the use of the operation for breech presentation. This rise has been fairly steady through the entire fifteen years with perhaps a sharper increase since 1942. The rate for the first three years, 1934-35-36, was exactly 5 per cent, and in the last three years it has risen to 12.3 per cent, more than doubled. In evidence of the value of such a trend we note that the corrected fetal mortality rate has dropped from 7.0 per cent to 2 per cent. It is interesting to point out here one of the features associated with a rising cesarean section rate which has been in evidence through the study. It will be noted (Fig. 5) that although the incidence of cesarean section for breeches rose from 10.5 per cent in 1943-44-45, to 12.3 per cent in 1946-47-48, there was no further reduction in the corrected fetal mortality rate. This suggests that rising cesarean section rates result in diminishing returns in so far as fetal salvage is concerned. Theoretically, we can say that each indication has its top incidence figure beyond which very little is to be gained. From these figures it would seem that in our cases at least there is little to be expected by increasing the cesarean section incidence for breeches beyond ten per cent.

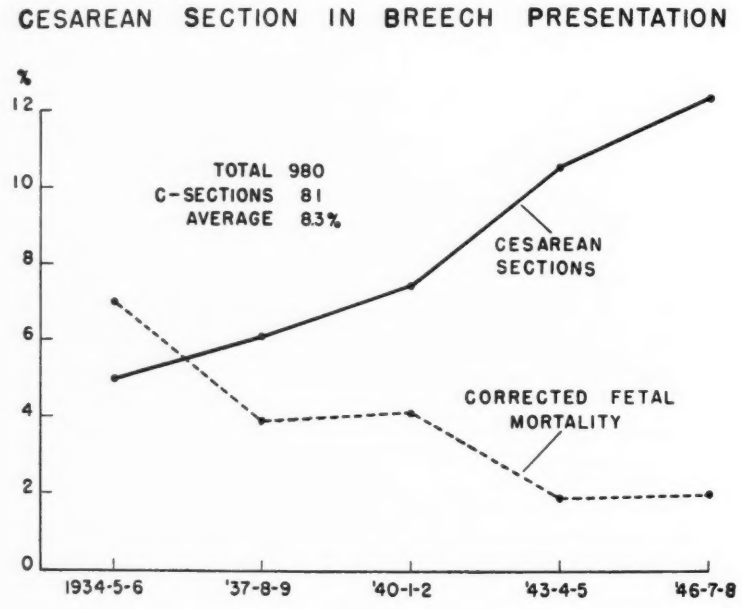

Fig. 5.

Malpresentation

Due to the small number of cases involved, the malpresentations, which here include transverse lie, face and brow presentations, are divided into the first eight and last seven years of the study (Table II). No significant difference is noted in the rates. This may be due to the small sampling. If the last three years are considered separately the incidence of cesarean section shows an increase with a fall in the fetal mortality rate. Whether this will be substantiated in a larger series remains to be seen.

TABLE II. CESAREAN SECTION IN MALPRESENTATION

	CASES	PER CENT	PER CENT CORRECTED FETAL MORTALITY
1934-1941	60	25.0	10
1942-1948	72	20.8	8.3
1946-1948	22	36.4	4.5

Fibromyoma of the Uterus

Fibromyoma of the uterus in our series has been treated by cesarean section in 15.6 per cent of the cases (Table III). There has been no significant change in the trend. Three maternal deaths have occurred in this group of 576 cases. The three deaths recorded briefly occurred as follows: In 1935, laparotomy at the seventh month for acute red degeneration in a pedunculated fibroid, mistaken for a twisted ovarian cyst; death from bronchopneumonia on the fourth day. In the same year, midforceps delivery at term followed by sepsis. In 1940, midforceps delivery; postpartum degeneration in fibroid, resulting in sepsis.

TABLE III. CESAREAN SECTION IN FIBROMYOMA

	CASES	CESAREAN SECTIONS	PER CENT
1934-1938	169	31	18.3
1939-1943	218	27	12.4
1943-1948	189	32	17.4

Prolapsed Cord

Since 1944 a new primary indication for abdominal delivery has appeared in our records (Table IV). Prior to that time the operation is not listed as a method of managing prolapse of the umbilical cord; since then eight cases are so recorded. As noted in Table IV, the corrected fetal mortality rate has been lowered from 18.9 per cent to 14.6 per cent. While this reduction in fetal mortality rate may not be proportional to the number of cesarean sections done and suggests that some of the infants delivered in this way might have been managed safely by the vaginal route, there is reason to believe that this complication will be treated by section with increasing frequency. This will be especially true when the cervix is incompletely dilated. Where minutes count this indication for abdominal section will make it mandatory that in the ideal obstetrical service the means for carrying out a rapid cesarean section be easily at hand.

The eight cases treated by cesarean section all resulted in living babies.

TABLE IV. CESAREAN SECTION FOR PROLAPSED CORD

	CASES	CESAREAN SECTIONS	CORRECTED FETAL MORTALITY
1934-1944	90	0	18.9%
1945-1948	48	8	14.6%

Cardiac Disease

Cardiac disease represents the only indication for which there is a clear-cut fall in the incidence of cesarean section (Table V). We have always been conservative in the management of these cases, but even more so in our recent experience. In the past four years we have done only one cesarean

section primarily for this condition. At one time it was felt that cesarean section, offering the possibility of sterilization, had certain advantages in selected cases but this is no longer a consideration in our present policy. Our experience confirms the fact that cardiac disease per se should never be a primary indication for the operation. We feel this way in spite of the fact that the fifteen cardiacs treated by cesarean all did well and that the three out of eight patients whose deaths occurred in the postpartum period were delivered by the vaginal route.

TABLE V. CESAREAN SECTION IN CARDIAC DISEASE

	CASES	CESAREAN SECTIONS	DEATHS FOLLOWING CESAREAN SECTION	TOTAL CARDIAC DEATHS
1934-1938	234	11	0	4
1939-1943	268	3	0	3
1944-1948	185	1	0	1

Summary

The trend for the cesarean section operations at Sloane Hospital during the past fifteen years shows a rise in the total use of the operation which has shown no discontinuity since 1942. This agrees generally with the averaged curve presented by four of the larger obstetrical services in Manhattan, and undoubtedly represents a valid broadening of the indications for the operation consistent with the safety factors contributed by recent advances in antibacterial and antishock therapy.

The increasing trends for the operation are noted most strikingly in placenta previa, followed by cephalopelvic disproportion, and breech presentation. Uterine inertia and fibromyoma show no significant changes in their trends. Malpresentation shows a very recent upward trend. Pre-eclampsia, accidental hemorrhage, and elderly primiparity which were also studied but not detailed show very irregular and unclassifiable trends. Cardiac disease shows a definite fall in the rate of cesarean section. Finally there has been added a new indication for the operation, namely, prolapse of the umbilical cord. This condition may well show an increasing incidence in the future.

Concurrent with the increasing incidence of the operation there is a definite shift in the proportion of abdominal deliveries, when compared to the number of vaginal operations. This is even more significant because there has been no change in the total number of all operative deliveries. The implication of this trend is that obstetrics is moving away from the area of vaginal obstetric surgery toward abdominal delivery. In support of this it can be shown that under ideal conditions the abdominal delivery is not more hazardous to the mother than the difficult vaginal operations and is certainly less traumatizing. The risk to the child is decreased as well. Against this trend it may be said that it will lead to unnecessary cesarean sections that are done when a vaginal delivery could have been effected easily and safely for both mother and child. Since it is axiomatic that uncomplicated vaginal deliveries will always be safer than abdominal deliveries, these unnecessary sections done for convenience or because of ignorance cannot be justified.

Discussion

DR. E. D. PLASS, Iowa City, Ia.—With such a reduction in the risk from abdominal delivery as has materialized during this past generation, it was inevitable that there would be some relaxation in indications for the operation. In my clinic the incidence of cesarean section has risen from 1.0 or 1.5 per cent to 4.0 per cent during the past twenty-three years, and I believe the increase has been justified and reasonable. By eliminating the physically difficult and mutilating vaginal deliveries that were so disastrous to both the mother and her child, the operation has served a specific and beneficial purpose.

On the other hand, no one has yet had the temerity to propose that all women be delivered abdominally, a tacit admission that cesarean section is more dangerous than vaginal delivery. Statistical data now available support the belief that neither the maternal nor the child mortality of abdominal delivery can be reduced to that of normal vaginal delivery. We are, then, confronted with what the economist recognizes as "the theory of diminishing returns"—there must be a point beyond which the lives and health of pregnant women and their children as a group would be prejudiced by further relaxation of the indications for cesarean section. Where this point lies would obviously provoke argument, but I am inclined, in view of our present information, to place it in the neighborhood of 5 per cent.

Another phase of the problem concerns the growing tendency to substitute abdominal delivery for induction of labor whenever an acute complication demands interruption of pregnancy, even though the latter is generally effective and certainly safer. When the complication is not likely to recur in a subsequent gestation, the use of abdominal delivery would seem rarely to be justified since it reduces the woman to what some have called an "obstetric cripple," an expression that emphasizes not only the artificial weakness of the uterine wall but also the mental state that militates against much further increase in the size of the family. Most women do not want more than two or three children, when the birth of each child demands a major abdominal operation, and many feel that one such experience is enough. The sociologic implications of families that do not provide numerical replacement of the breeding stock, the parents, are obvious.

Since many of the recognized indications for abdominal delivery are essentially fetal in nature, I must confess some curiosity about the total uncorrected child mortality in Dr. D'Esopo's series. I inherently dislike corrected statistics, and particularly in cesarean section, where the indication for the operative intervention is so often fetal. I would be inclined to view the extraction of a child with a congenital anomaly incompatible with extrauterine existence or of a nonviable premature infant as a therapeutic failure, unless the operation were actually life-saving for the mother, and there are really few such instances.

We should then, I feel, be cautious about lending the prestige of this Society to any marked and sudden extension of the indications for cesarean section beyond the point where the operation truly serves the best interests of the two patients involved.

DR. W. C. DANFORTH, Evanston, Ill.—I wish to present some figures concerning cesarean section from our service at the Evanston Hospital. These figures are taken from a study of the last 20,000 cases which was made by my colleague, Dr. R. M. Grier. The number is actually 20,811. The great majority of these were private patients. The staff consists wholly of obstetricians who are members of the Department of Gynecology and Obstetrics of Northwestern University. I am in accord with the opinion which has come from a number of clinics in the past two or three years, that cesarean section should be used more liberally in the management of placenta previa. But there is too great a tendency in some places to broaden the indications too greatly. In a recent visit in a large city I was told by a member of the obstetrical staff of a hospital which is regarded in that city as one of the best, that the incidence of cesarean section in that institution varied from year to year from ten to twelve per cent. This seems entirely out of line and would indicate that many problems are being solved by section which might be dealt with by other obstetrical means.

In the 20,811 cases in our service there were 856 sections, or 3.26 per cent. The maternal mortality in this series of sections was 0.93 per cent.

Many physicians, chiefly those whose obstetrical experience is not extensive, seem to feel that abdominal delivery is a rather certain way of obtaining a living child. Because of the indications for which many sections are done this cannot be so. Abruptio placentae, placenta previa, and severe toxemia take an inevitable toll. The fetal mortality in the group of sections was 8.2 per cent. This may be compared with the fetal mortality after midforceps operations, for example. This was 2.2 per cent. That operative delivery was not avoided may be indicated by the incidence of outlet forceps delivery which was 50.2 per cent.

Cesarean section is an operation of tremendous importance. This fact, however, should not cause us to advocate it when sufficient indications do not exist. The mortality of section, even in well-staffed institutions, is usually somewhat greater than that of major abdominal gynecological procedures. While our mortality rate of 0.93 per cent is a satisfactory figure it still is higher than our mortality in either total abdominal or vaginal hysterectomy. In a few cases only delivery through the vagina was permitted after cesarean section. Our over-all obstetric mortality in this group, including all operative procedures, and including some deaths from disease present during pregnancy and parturition, was 0.091 per cent. While the danger of cesarean section is notably less than it was years ago, it is still an operation which carries an appeciable mortality. While I am fully appreciative of its worth, and we are all convinced that we cannot do without it, I would express a word of caution concerning a too great broadening of indications.

DR. EDWARD A. SCHUMANN, Philadelphia, Pa.—Whenever, I hear a paper like this thoughtful, philosophical presentation of Dr. D'Esopo, I am mentally torn by the chart showing the tremendous number of cesarean sections done in another clinic and I wonder if in my own clinic possibly a similar chart would reveal not quite enough sections done. As I watched Dr. D'Esopo's graphs I was impressed by the 6 per cent incidence of section for cephalopelvic disproportion. Frankly, I do not believe that cephalopelvic disproportion of appreciable degree exists in 6 per cent. I think a little teaching of the mechanism of labor to our medical students might lower this indication markedly.

I am in entire accord with what Dr. Danforth has said about cesarean section in the presence of hemorrhage. Section incidence cannot rise too high in severe placenta previa to suit my own idea.

There are two points I should like to emphasize: cesarean section in the presence of malpresentation and cesarean section in the presence of a dead baby. Dr. Plass has spoken of the therapeutic failure if a dead baby were delivered by cesarean section. That in general is quite true, but what about the neglected, impacted transverse presentation in a patient who has had attempts at delivery from below and finally arrives at the clinic a bad surgical risk? She often is also a bad obstetric risk with a dead baby, and I have yet to see the obstetrician, be he young or old, trained or untrained, who has had sufficient experience with difficult embryotomies to do them well. This is a formidable procedure at best and, after the passage of one or two hours, one may find that the patient is in serious condition from shock and blood loss and exhaustion, and embryotomy may or may not have yet been accomplished. With the enormous improvement in surgical technique through extraperitoneal section it is in our experience—and we now have some twenty-six cases to record—a perfectly safe procedure for the mother to do an extraperitoneal cesarean on a dead impacted transversely presenting baby, to extract the baby through the uterine incision by embryotomy, if you please, under the eyes without difficulty, with much less risk to the mother, and I advocate this procedure in this indication.

I fear we are a little "loose" with our cesarean sections. It is so perfectly simple to do the operation under local anesthesia two, three, or four times. I find that these patients who have been operated upon under local anesthesia do not object to repeat sections, but I do believe that we must guard against too ready a tendency to perform cesarean section in the presence of a very dubious cephalopelvic disproportion.

DR. NORMAN F. MILLER, Ann Arbor, Mich.—I would like to ask the essayist what he does with the fibromyomas for which cesarean section was indicated?

DR. GEORGE KAMPERMAN, Detroit, Mich.—Having been trained as a conservative by a conservative teacher, it has been very difficult for me to rid myself of conservatism and I must confess that I have resisted a great many of the procedures that took us away from conservatism. I have embraced some of the ideas of the newer obstetrics, but I feel resistant toward becoming too radical.

I have often seen the indications for cesarean section labeled after the performing of this operation. I would make a plea for more careful preoperative diagnosis of the indications. For instance, too often cesarean sections are performed for bleeding without a precise diagnosis of the cause of the bleeding. The fact that occasionally the roentgenologist does not properly diagnose the position of the placenta gives some obstetricians the attitude that roentgenologic examination does not mean much, and they are afraid not to operate. The same is true of cephalopelvic disproportion. A patient may have labored for a long time and disproportion comes into the mind of the obstetrician. In fact, it amounts to a fear in the minds of many men. The cesarean section is then performed just because of fear. It takes a great deal of experience to develop good judgment and fortitude so as not to be led into these radical operative methods simply because we are afraid.

DR. JOSEPH L. BAER, Chicago, Ill.—There are a few points which we carry out in our institution which I think it might be well to convey; most of you probably do the same things but lest you do not I want to emphasize them.

The cephalopelvic disproportion group is always debatable. We have an inviolable regulation in our department at Michael Reese Hospital that at the time of section the inlet must be measured while the abdomen is open and the biparietal measurement of the fetal head is taken immediately after delivery. At the regular monthly meeting of our department every cesarean section is analyzed in detail and particularly as to the indications. We emphasize the necessity for a recorded preoperative indication before a patient is subjected to cesarean section. It happens that every once in a while our cesarean section percentage goes up, and after the following monthly analysis it goes down.

I believe that cesarean section for any indication whatsoever without a vaginal examination is subject to incomplete preoperative diagnosis. We refuse to be intimidated by the anxiety that accompanies a vaginal examination preceding cesarean section. And we not only permit it; we insist upon it.

DR. NELSON B. SACKETT, New York, N. Y. (By invitation).—I would like to make one comment concerning the value of extraperitoneal cesarean section in cervical dystocia cases. I know I am on dangerous ground in using that word. In 1940 I reported the incidence of true cervical dystocia. In 8,000 confinements in Woman's Hospital in New York, I threw out seven out of eight so-called cervical dystocia cases and retained one per cent, or 80 cases of true cervical dystocia.

Along with Dr. Schumann, I would like to put in a plea for the use of extraperitoneal cesarean section in these cases. I feel that having the extraperitoneal cesarean section "up your sleeve" enables you to exercise conservatism along the line Dr. Kampermann mentioned: to have the courage to let the patient labor on a few hours longer, knowing that you can still get out of a bad situation with extraperitoneal cesarean section. My study in 1940 showed that most of these patients were safely delivered from below, usually by medium forceps and occasionally with the blades inside the cervix. In those cases where we guessed wrong, the extraperitoneal cesarean section gave excellent results for mother and baby.

DR. D'ESOPO (Closing).—I am inclined to agree with Dr. Plass that the cesarean section must be looked upon as a crippling operation from the point of view of future pregnancies. Many of these patients have only one baby. In 1,000 cases reported last year only sixty-four were delivered of their third or fourth babies. The sterilizing aspects of the operation, however, are not in conflict with the American norm of family size. With increasing

safety of the operation we are permitted greater latitude in the number of children that a woman may have before sterilization is carried out.

I also agree that the induction of labor, especially in medical complications such as toxemia, vascular disease, and diabetes, may become a competing procedure. We have been inducing labor in these cases with Pituitrin infusion and have been impressed with its value. It gives us a trial induction which does not compromise the later section if this becomes necessary. We will continue to explore the possibilities of this procedure with interest.

With reference to the decreased returns of the operation in terms of fetal salvage, I have been impressed with the fact that the economic law of diminishing returns applies to cesarean sections as Dr. Plass stated, but it varies for different indications. For placenta previa, the fetal salvage may increase as the section rate increases until a figure of near 90 per cent is reached, whereas, in breech presentation, the salvage rate does not improve to any extent after a section rate of 10 per cent. For the entire group, the top rate beyond which the fetal return is no longer appreciably increased is probably in the neighborhood of 6 per cent, varying with the type of service. This idea may be expressed in another way by saying that if we go beyond a certain ideal top cesarean section rate, the number of mothers that will require section to save one baby becomes too high.

Dr. Plass' disagreement with corrected fetal mortality rates which were used can be answered by saying that unless some correction is made it is difficult to say that the fetal samples are uniform. For example, if the lifesaving value of one operation is to be assessed against another, you start with a group of babies that is salvageable to begin with. I corrected the figures with the view that the lowest theoretical mortality rate could have been zero and any mortality above that measures the comparable failures of the procedures employed.

Dr. Schumann said that a 6 per cent incidence of cephalopelvic disproportion among the primiparas was too high; he does not believe there are that many cases with that indication. He is correct if he is talking about absolute degees of disproportion, but we are dealing here with relative degrees of disproportion. Our concept of disproportion keeps on changing; it is not a static term. To justify the figure we can show that by raising the incidence of cesarean section for cephalopelvic disproportion from 2 to 6 per cent during the last fifteen years, we have reduced the midforceps rate by exactly the same margin. As a consequence, we have saved many more babies by doing the extra 4 per cent sections in these primiparas than we could have if we had delivered them by force through the vagina.

With every new advance in surgery which makes for greater safety to the mother, the variables involved in the concept of cephalopelvic disproportion need redefining. We have certainly progressed to the point where it is unjustified to attempt operative vaginal deliveries that will result in major trauma to either mother or baby. We are approaching this ideal of atraumatic obstetrics without losing mothers, by raising the incidence of cephalopelvic disproportion in our clinic to the figure that Dr. Schumann criticized.

Dr. Miller asked about our cases with fibroids. We do sections on 15 per cent of our total group that go through pregnancy with fibroids. This relatively small group of patients, therefore, is likely to have either very large or obstructing fibroids and as a consequence most of them were treated by hysterectomy.

THE HISTOGENESIS OF UTERINE MYOMAS*

OTTO H. SCHWARZ, M.D., AND SETH WISSNER, A.B., M.D., ST. LOUIS, MO.

(From the Department of Obstetrics and Gynecology, Washington University School of Medicine)

MANY years ago one of us (O. H. S.) studied a specimen of a uterus of a nulliparous 18-year-old girl, which showed very small myomas. Scattered throughout the wall were many small foci of growths which represented myomas in early stages. It was decided from the study of this uterus that these myomas originated from small arterioles and very small arteries. At that time, as now, it was generally believed that the most common origin of myomas was from adult cells or germ cells in the muscle fibers. This idea has been strongly supported by none less than the late Robert Meyer. Statements in the modern texts on gynecological pathology will state that this is an undecided question. We, therefore, thought it opportune to reinvestigate the entire subject.

From a review of all the literature it was found that the subject had been thoroughly studied by Robert Meyer[6] and Hans Albrecht.[1] In Meyer's review he discussed all the early theories concerning the cell origin and referred to several writers who considered an immature cell as the start of this development. Meyer dismissed this idea with the suggestion that the lesions arise from the normal uterine muscle, and substantiated this with an illustration showing the latter characteristics. He mentioned that blood vessels, especially the arteries, had been considered as a source of origin. He mentioned the work of Klebs, Roesger, Gottschalk, Stern and others. He stated that Aschoff, Faber, Willy, Becker, and himself felt that the smallest myomas did not have any relationship to the blood-vessel wall. Meyer also stated that Sakurai and Aschoff studied myomas 0.06 to 0.02 mm. in size, and found that they were not associated with the blood vessels. Capillaries appeared in those 0.2 mm. in size, but were regarded as secondary. There were no illustrations in Aschoff's work. We studied areas of this size, namely, 0.06 to 0.02 mm., and one cannot say for certain that these are going to be myomas. In these the relationship to the blood vessels can be demonstrated, but they are too small to be considered as initial lesions. Meyer mentioned that Stern, in seedling myomas 0.7 to 1 mm., found proliferation of muscle cells from the media; but says this is entirely contrary to most prevailing opinions. Albrecht, in a similar review, stated that no exact definite piece of work had been carried out which would settle the question of origin conclusively. He favors the origin from the uterine muscle and he points out that the uterine muscle cell has a great propensity for growth which is exemplified by its marked enlargement at full term in pregnancy. He feels that if this phenomenon is not frequently carried out a tendency could be developed in these muscle cells to produce myomas as a result of this prolonged resting period. To this point we shall refer later. Since 1930 the literature on the subject has been rather fragmentary

*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

and articles that have some bearing on the point under discussion have appeared by Faulkner,[2] von Jasche, Horta, Homgren, Ravenna, Lipschütz.

Returning to the inactivity of uterine muscle cells as a possible factor in the development of myomas we would like to call attention here to the fact that during pregnancy the uterine circulation undergoes a much greater hyperplasia and hypertrophy comparatively than the muscle cells themselves. In the process of involution, the involution of the muscle cells is very nearly complete by six weeks and definitely so by eight. In the involution of the circulatory system, three to five months are required and unfortunately, very frequently, this is not complete, leaving certain old vestiges, giving rise to the condition known as chronic subinvolution, first accurately described by Fletcher Shaw. During pregnancy the increase in the caliber of the uterine vessels increases many fold as early as the sixteenth week, particularly at the placental site, continuing to enlarge until near the end of term. This stimulation can be directly attributed to the action of estrogens and progesterone, the two hormones acting together to bring about the final picture.

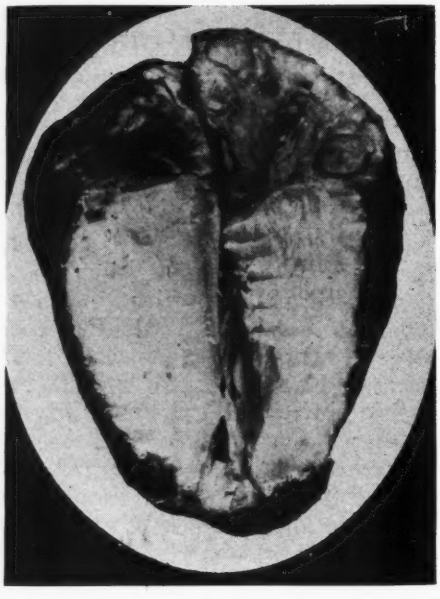

Fig. 1.—Nulliparous uterus; Age 18 years; supravaginal hysterectomy. Photograph slightly reduced. Uterus actually about 50 per cent enlarged. The walls are studded with small discrete myomas; the largest about 1 cm. in diameter is seen in the upper right side of the picture. The chief increase in size is due to very numerous foci of growths from microscopic size to 1 mm. throughout the entire uterus. (Specimen presented by Dr. E. Lee Dorsett, March, 1920.)

Many investigators have produced hyperplasia of the endometrium with estrogens alone. No attention, however, has been placed on the character of the uterine blood vessels under these conditions. It has been casually noted in the present study that in uterine walls in which there occurs a hyperplasia of the endometrium, particularly exhibiting the Swiss cheese pattern, invariably there is a marked hypertrophy and hyperplasia of uterine vessels in general, but particularly in the middle third of the uterine wall. This observation is being fur-

ther investigated and will be presented in detail in another paper in the very near future. Clinically, sterility has frequently been mentioned as a factor in the incidence of myomas. Cullen called attention to this quite strikingly in his monograph with Kelly in 1910. He points out that in his material about 50 per cent of the patients were sterile. Others had full-term pregnancies, but it is very striking that the number of pregnancies in these individuals was definitely limited to one or two. Further, if myomatous growths do not occur clinically by the age of 50 years they seldom develop. Also, if they are recognized after the menopause and are causing no symptoms and they are not removed, seldom do they show any great propensity of growth. Again, during pregnancy

Fig. 2.

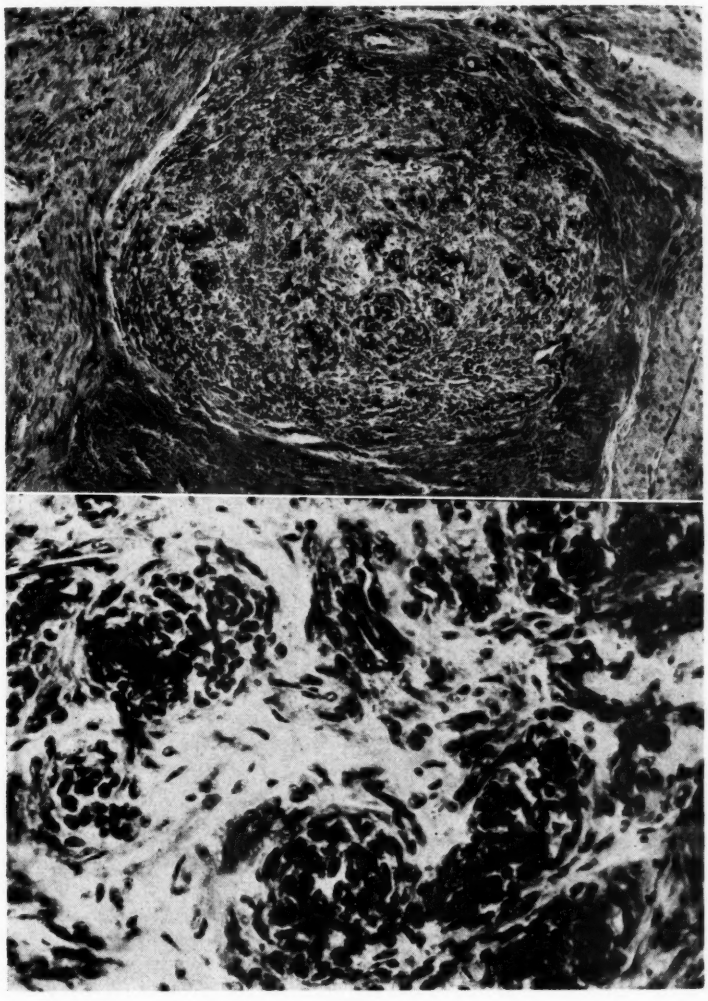

Fig. 3.

Fig. 2.—Section from Fig. 1. Shows a small very cellular myoma 0.4 mm. clearly encapsulated. The darker areas with cells in concentric arrangement have their origin from very small arteries. Myoma, 0.4 mm. in diameter.

Fig. 3.—High power of Fig. 2. Lumina of vessels in concentric areas readily compressed, but note the lumen is quite apparent in a slightly larger vessel in lower center of picture.

myomas seem to take on increased activity and even with this increased activity do not cause the patient any noticeable difficulties unless they undergo red degeneration, a type of degeneration which is seen at other times but more especially during pregnancy. If a woman delivers, having a myomatous uterus, it has been noted that these myomas will undergo involution as well as the uterus and it is stated by some that they actually disappear. This shrinking in size has also been noted from time to time in myomas which are recognized after the age of 50 years.

Fig. 4.

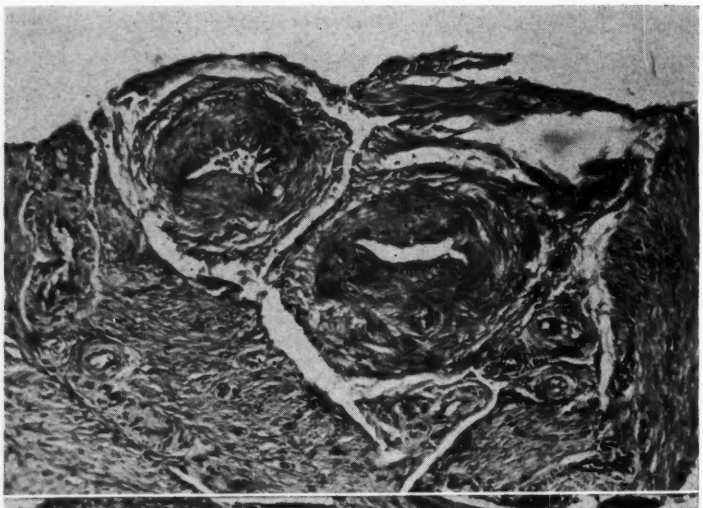

Fig. 5.

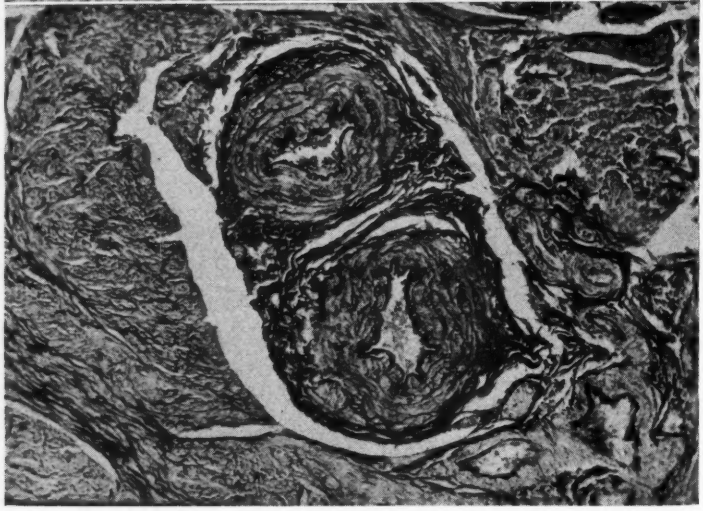

Fig. 4.—Normal arteries of good size, middle third of adult uterus. Note number of nuclei in media and compare with subsequent pictures of marked hyperplasia of vessels.

Fig. 5.—Same field as Fig. 4, orcein van Gieson stain. Elastic tissue stains dark brown, muscle, yellow, connective tissue, red. In black and white reproduction elastic tissue appears black, muscle light, connective tissue also black. Note normal internal elastic membrane, fine elastic tissue in light media, in outer periphery dark adventitia, which actually stains bright red in contrast.

A question which is immediately asked when one attempts to emphasize the uterine blood vessel origin is, "Why do not myomas grow in the media of blood vessels in general?" They actually do, but only on rare occasions. Outside of the uterine body there are very few blood vessels which are not carrying out their almost full physiological function constantly. The vessels in the kidneys may be a slight exception because no doubt during pregnancy an increased volume of blood flows through them as has been shown experimentally. The ovarian vessels, of course, are almost continually in a state of hyperplastic activity and retrogression. Apparently, both the uterine and ovarian vessels

Fig. 6.

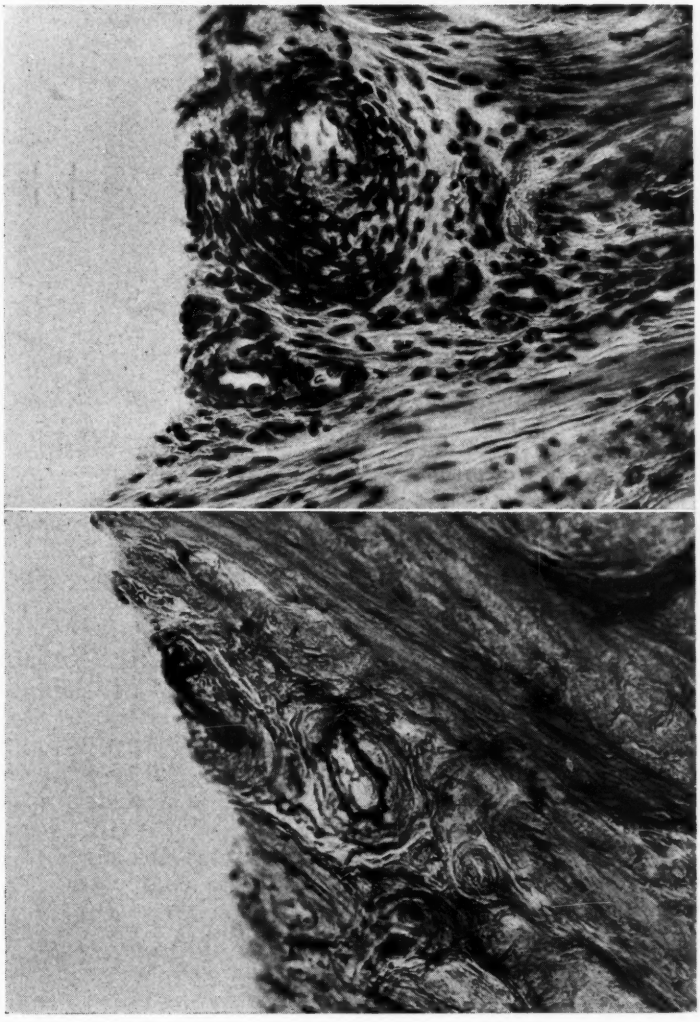

Fig. 7.

Fig. 6.—Shows two small arteries (hematoxylin and eosin stain). Both have same size lumen. Upper one shows marked proliferation in myoma-like fashion, lower presents no special activity.

Fig. 7.—Same field as Fig. 6. Orcein van Gieson stain. Note internal elastic membranes both same size, upper and outer compressed but similar in size; this is the smaller vessel in Fig. 6.

are stimulated hormonally in a more selective manner. Another question that arises is, "Why do not myomas appear more frequently in experimental and certain domesticated animals?" It is well known that they occur and this subject is reviewed in the excellent monograph of Feldman. Our answer to that fact is that the life span of these animals is so short that it is not compatible with the growth of myomas which in the human being is also well known to be comparatively slow.

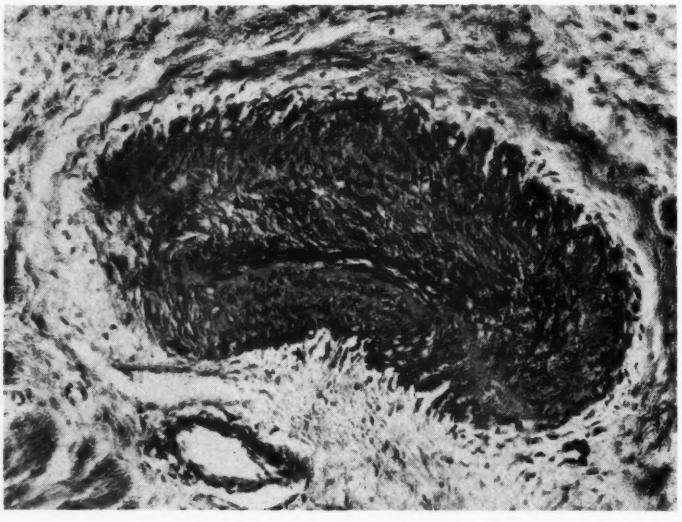

Fig. 8.—Large hypertrophied and hyperplastic artery. Note this type of hyperplasia produces a more fibrillated structure, such as is seen in many myomas. Note the proliferating media going into the adventitia, much like the extension of cells in a tissue culture.

Material

We selected from our files sections of uterine walls as they appeared. These sections included the entire uterine wall from endometrium to peritoneum. Newer material was studied to the extent of about 100 uteri because we wished to stain the walls not only with hematoxylin and eosin but with orcein van Gieson stains. It had been the routine of our laboratories for a period of over seven years to stain the uterine wall with both stains, particularly to assist in making a diagnosis of so-called subinvolution. A total of some 750 specimens of the uterine wall were studied; more were available, but we feel sufficient evidence was gathered from this first series. In studying these sections we naturally looked for small foci of growth. Numerous small areas 1 mm. and less were found; a great many that measured between 2 mm. and 1 cm. were found as well. A certain number that were seen reached as high as 2 cm. in diameter.

In the early part of the study we soon found out that it was far less difficult to determine whether an early myomatous development came from the media of vessels, especially the arteries, than from the muscle per se. We feel our illustrations will bear out this point and, therefore, without going into any great detail concerning our findings, we felt it would clarify matters to give rather detailed legends with each illustration. In myomas which we felt came from very small vessels the structure was rather consistent. Such lesions developed into very cellular myomas; the cells showed thickened and blunt-end nuclei with comparatively little cytoplasm. In these lesions numerous

foci herded themselves together to form small encapsulated nodules. These myomas in developing actually received their nutrition from the vessels which formed them. Hypertrophy and hyperplasia of the larger vessels, especially those of the middle third, were common findings. This picture was controlled by the fact that in certain uteri the vessels for their size appeared as would other vessels in any other part of the body. The hyperplasia was particularly conspicuous in the larger arteries and veins, and there a different type of structure developed. This consisted chiefly of many elongated deeply staining nuclei running more or less in a fibrillated manner. The periphery of the vessel was involved first, then its center was involved, and finally the original lumen of the large vessels was obliterated. In order that these masses can continue to grow,

Fig. 9.

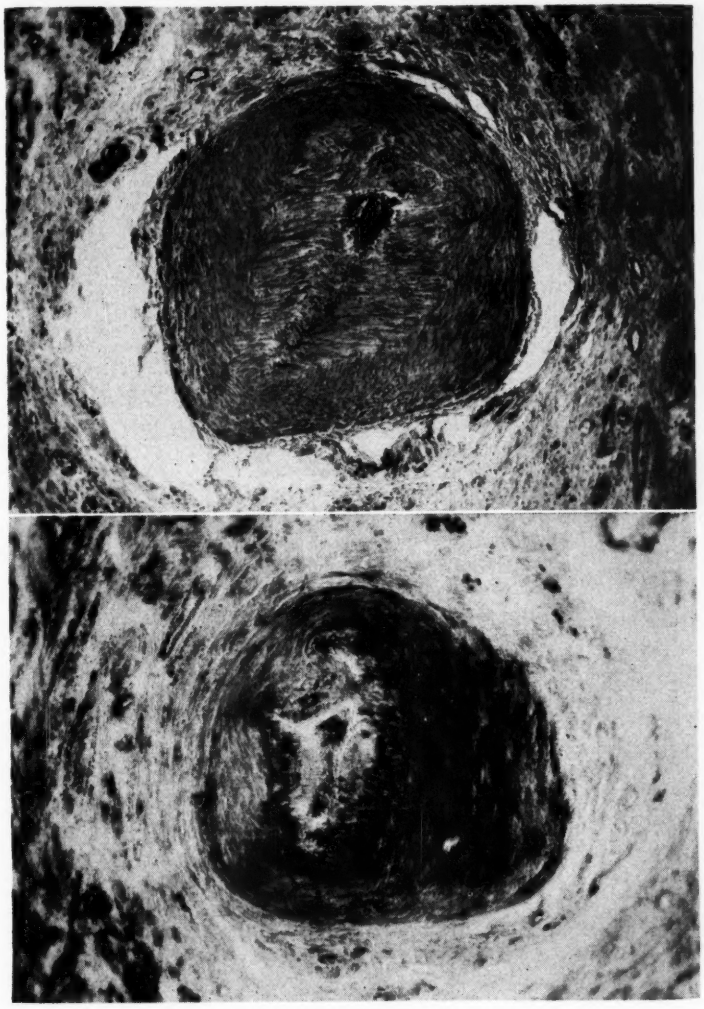

Fig. 10.

Fig. 9.—A very cellular circumscribed clearly demarcated structure made up of hyperplastic muscle cells 0.6 mm. in diameter, very fibrillar in type. Note the center opening of vessel filled with blood.

Fig. 10.—Orcein van Gieson stain, same field as Fig. 9. Note the almost complete destruction of the internal elastic membrane with the diffusion of elastic tissue chiefly to the right. This is not comparable to changes in chronic subinvolution (see text).

the blood supply must come from the existing vasa vasorum which in turn must undergo hyperplasia if sufficient nutrition is to be supplied. This point is emphasized by the fact that even in small masses of this kind (1 or 2 mm. in diameter) the center of these areas occasionally shows some early hyalinization. One such case is clearly demonstrated in our illustrations (Fig. 11).

There is a third pattern of myoma which we have seen in the series as well, and these are more or less encapsulated masses which we feel come from the walls of fair-sized veins. Larger myomas with this pattern are also encountered. We

Fig. 11.

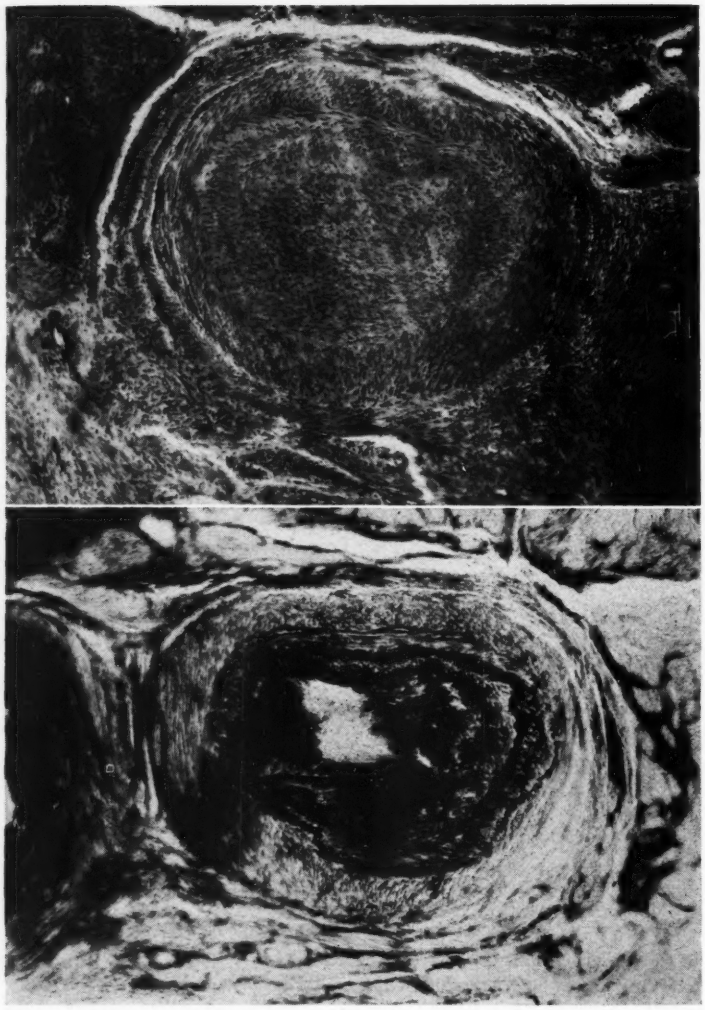

Fig. 12.

Fig. 11.—Encapsulated mass of myomatous tissue 0.6 mm. showing thin spindled type of cell, characteristic of the cells seen in markedly hyperplastic uterine vessels. Origin from large artery, note the beginning hyalinization in the center. Nutrition of such lesions must be taken up by hypertrophic vasa vasorum; if this is not sufficient, early hyalinization occurs. This is entirely different from the small artery development which takes care of itself as growth continues.

Fig. 12.—Orcein van Gieson stain, same field as Fig. 11, proving it to be an artery involved. Reduplication of internal elastic membrane indicates multiparity (chronic subinvolution), but note how elastic membranes are broken up and diffused as seen in Fig. 13.

have illustrated two (Figs. 13 and 14). The search for lesions developing from the muscle fibers themselves was diligently carried out. Many suggestive patterns were seen, but we state emphatically that it is far easier to find evidence of these early lesions coming from blood vessels than from the muscle tissue itself. Of course, when the myoma develops to any size greater than 2 cm. it is almost impossible to make any definite assertions as to origin, with one exception. We have noted in myomas from 2 mm. to 1 cm. in diameter that they contain many arteries and veins, but the veins are not readily distinguishable. Perhaps the reason is that the veins are more readily compressed, and their walls intimately incorporated in the substance of the growing tissue. Frequently the vessels in

Fig. 13.

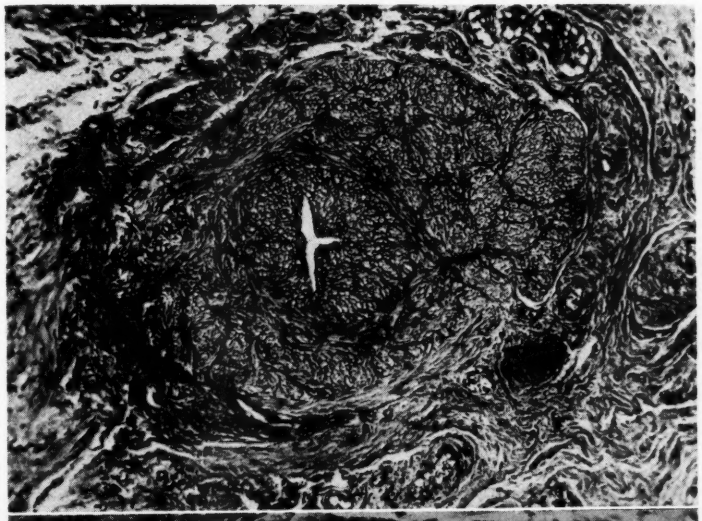

Fig. 14.

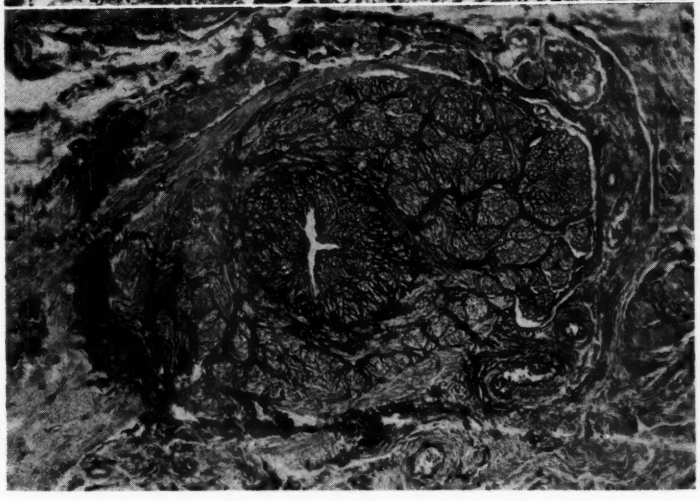

Fig. 13.—Circumscribed nodule 0.4 mm. of myomatous tissue, pattern of which is sometimes seen in larger myomas—center lumen of a vein, muscle bundles in vascular form; sprinkling of large muscle cells throughout area; marked cellular activity in walls of tiny arteries in area immediately surrounding mass.

Fig. 14.—Same area as Fig. 13. Orcein van Gieson stain. Note circle of irregular elastic tissue at the periphery of original vein (sometimes referred to as "the external elastic membrane" in vein). This diffuses into the original thin wall as well as into the surrounding hypertrophied area.

these small myomas show a very marked proliferation of their media made up entirely of deep-staining, closely packed cells with a tendency to invade the neighboring matrix. It would seem that this might be considered under these circumstances as the source of their original development.

In studying areas associated with large arteries the media shows marked proliferation. A good-sized internal elastic membrane in varying stages of disintegration can be demonstrated. The internal elastic membrane is broken by the activity or pressure of these cells and can be demonstrated as present in the wall of such an artery in a diffused state (Fig. 10). The character of this lesion is not to be confused in any way with the abnormal distribution of the elastic tissue in the picture of subinvolution of the arteries.

Fig. 15.

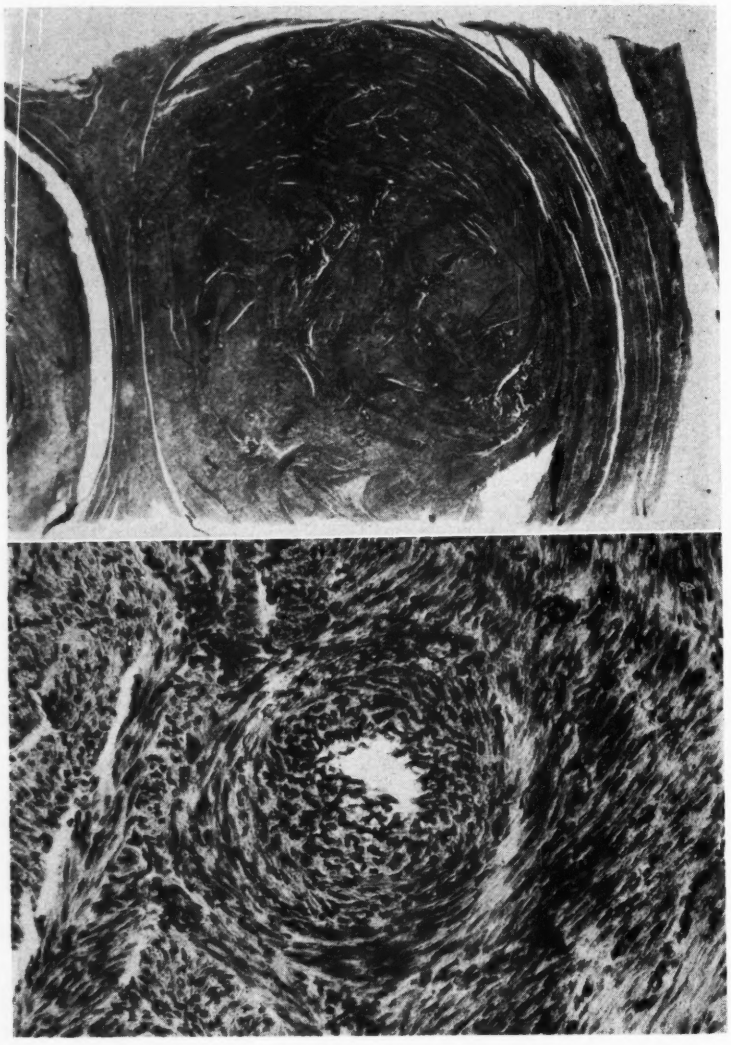

Fig. 16.

Fig. 15.—Low power, encapsulated intramural myoma, 8 mm. in diameter, rich in small arteries, which are hypertrophied, a lesser number of veins visible.

Fig. 16.—High power of Fig. 15. Single artery, markedly hypertrophied, with striking increase in hypertrophied cells. Note the concentric pattern in the periphery of the vessels. No adventitia.

Conclusions

We conclude from the study of our material that myomas commonly arise from small arterioles containing smooth muscle in their walls, small and large arteries, and from both large and small veins. We feel that it is much more difficult to show evidence that they actually arise from muscle bundles; and although we made considerable effort to demonstrate lesions suggestive of this origin, we found none impressive enough for illustration. The very close relationship in most instances of small myomatous areas to the blood vessels, and, on the other hand, their actual development from the blood vessels, make it very difficult to account for muscle-fiber cell origin, because of the difficulty in determining landmarks, which one can readily do in the case of the blood vessels. We found that the illustrations in the literature were meager, mostly not clear, and almost no photographs were found; consequently we feel that no clear-cut illustrations have been presented to date. We do not question the fact that muscle-fiber origin may occur as many careful observers have concluded, but we question very much that the uterine muscle fiber per se plays any great part in the development of myomas. We acknowledge that this origin may exist, but we feel that the blood vessel origin is the more common.

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Discussion

DR. ROBERT L. FAULKNER, Cleveland, Ohio.—Positive determination of the origin of a common tumor such as uterine myoma would be a landmark in gynecology. Dr. Schwarz presents evidence that myomas, more frequently than is usually thought, originate from blood vessels, particularly arteries. From the mere nature of the growth of myomas, there may arise doubt that this matter is irrevocably settled and I am sure the author himself has no such idea.

Many years ago, John Sampson spoke of the "basket" pattern of arteries surrounding the young myoma with branches here and there penetrating its substance and furnishing its nourishment. The impression of probable function gained from such a pattern is that the vessels are called into being to feed a parasitic body suddenly arising in their midst.

As myomas enlarge even slightly, most of them, not all, become veritable masses of blood vessels which inject as arteries, and here it seems to me is the crux of the situation in interpreting proliferative changes in vessels. Since there is and has to be amazing growth of blood vessels within the tumor to keep pace with its increasing size, the interpretation of proliferative cellular changes within the vessels themselves has to be made with the question in mind as to whether the activity represents tumor growth toward the usual nonangiomatous myoma kind, or is simply reproduction of themselves as blood vessels.

The author has definite ideas as to why veins do not inject in myomas, and he may be right that compression is a factor in producing failure of injection, rather than that

veins do not penetrate the tumor. Histological study of a tumor, however, should not be relied upon too much for identification of vessels because it is generally taught that young, and even older, blood vessels of either series in a growing tumor, may all look alike. It is to be pointed out that veins are easily injectable in the trabeculae of a compound myoma, and on the other hand in adenomyoma, which is usually under no great tension within its contained space, veins again fail to inject as in the ordinary myoma. Furthermore, in a tumor which has been the victim of such a serious obstructive vascular accident as acute red degeneration, dilated lymphatic spaces should be and are present, and complicate the problem of positive identification.

DR. EMIL NOVAK, Baltimore, Md.—Dr. Schwarz, in the presentation of his paper, initiated a method of presentation which might well be emulated: State your conclusions first, and then try to prove them with your slides. The orcein-van Gieson technique which Dr. Schwarz has so effectively employed since his early days of study in the German laboratories has stood him in good stead in the present investigation. As I watched his slides, however, I had the distinct feeling that they threw much more light on the behavior of blood-vessels within myomas than they did on the histogenesis of these tumors. The thickening of the muscularis seen in many of the blood vessels was often localized, giving one the impression that the picture was due simply to tangential section, much as we see in the study of blood vessels elsewhere, especially when the course of the vessels is not straight but more or less curved or spiral. I am glad that Dr. Schwarz did not inject the endocrine factor in his discussion of the origin of myomas, for the evidence for this is pretty slim. The question of whether these tumors have their source in certain rather immature cells of the uterine musculature, or from the muscularis of the blood vessels, is still an open one, but Dr. Schwarz's study has been a provocative one, and his conclusions have been very conservative.

DR. SCHWARZ (Closing).—I did not mention in the paper the physiologic hyperplastic changes in the normal uterus during pregnancy, for example. First of all I want to say something about the adenomyosis case which Dr. Faulkner injected and which showed no veins. Any one can take an ordinary section of a normal uterine wall and notice that the arteries are outstanding but you will have to look more carefully for the veins. This is illustrated as well in the pregnant uterus. The veins develop along with the arteries and you see them as outstanding accompaniments whereas in the ordinary uterine wall the veins are compressed and not so conspicuous histologically as are the arteries.

Also, I did not discuss the endocrine problem, but I believe that in the origin of myomas there is some abnormal stimulation of estrogen and progesterone. In that connection I can cite a case of a uterus of a woman aged seventy-eight years. She had received estrogen and progesterone for the past two years by Masters of St. Louis, who is making special observations on the effect of estrogens and progesterone on the aged. These slides show hyalinization present very strikingly at this advanced age and throughout there is proliferation of new cells in the media of the vessels.

THE FEMALE BLADDER AND URETHRA BEFORE AND AFTER CORRECTION FOR STRESS INCONTINENCE*

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(From the Georgetown University Hospital)

ON JUNE 8, 1944, approximately five years ago, simple vesicourethral suspension by the suprapubic route as described by Marshall and his co-workers[1] was first tried for the correction of female urinary stress incontinence. Their experience with the procedure from that day to May 11, 1948, a period of almost four years, was just recently published.[1] That report includes the story of how the idea was conceived, the description of a preoperative test designed to make the selection of candidates for the operation most suitable, the description of the technique of the operation itself, and an analysis of the results of the operation. No formal attempt was made by the authors to explain or evaluate the mechanics by which that particular operation restores or improves urinary control.

Fifty patients constituted the basis of their clinical analysis, thirty-eight of whom were women operated upon specifically for urinary stress incontinence. Of this latter group, it is noteworthy that twenty-five, or two-thirds of them, had had a total of forty standard operations which routinely should relieve urinary control, but had failed in these cases. After simple vesicourethral suspension was performed upon the thirty-eight women with stress incontinence, the incidence of complete failures was 8 per cent. In 74 per cent of the same group the result was entirely satisfactory and in 18 per cent was considered definitely improved. Wilfred Shaw[2] makes the comment that "vaginal operations for the relief of stress incontinence have one factor in common —the originators always claim good results." The approach by Marshall and his co-workers is not per vaginam. The claim, however, runs true. In fact, as our experience enlarges, it may be found that simple vesicourethral suspension by the suprapubic route may yield better results than some of the commonly used vaginal operations. Its worthiest indication as the procedure of choice is in cases of recurring incontinence where repeated vaginal operations have failed and have produced so much scar tissue that further attempts through the same route would be almost impossible.

For the past eighteen months, the author's experience and observations with this procedure have expanded by intensively studying twelve additional patients with the complaint of exertional incontinence. Interest and attention were focused on the disclosure of factors contributing to and explaining the mechanism of the procedure's success. It is the purpose of this communication to present an evaluation of the clinical and anatomical findings that were further accumulated before and after operation in the course of this study.

*Presented, by invitation, at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

The selection of the cases for operation was made without in any way altering the preoperative test as originally described. The primary complaint in every instance was urinary stress incontinence. With but a single exception, all of the patients had borne one or more children. Four of them had had vaginal repairs of the Manchester type with plication of the vesical sphincter. Another four had a urethrocele combined with a slight to moderate cystocele. Two were elderly women (aged 60 and 75 years) totally incontinent without any degree of prolapse and with only a small degree of anterior vaginal wall relaxation. One had no clinical evidence of any loss of support of the urethra or of the vagina. The last or twelfth patient was of special interest. She had had a total hysterectomy for a submucous myoma and at the same time a vesicourethral suspension for exertional incontinence. Ten weeks later the loss of urinary control recurred and became progressively worse. She was recently subjected to a second suspension operation. This case presented the opportunity to search for the cause of the failure of the first operation and will be referred to later.

A few steps in the technique of the operation have been altered in this group, but not radically. In the original description, the first series of sutures placed laterally and equidistant along the course of the urethra between the external meatus and the vesical neck was made to include a portion of the wall of the urethra as well as the wall of the vagina. Now these sutures are directed to exclude the urethra and to include a stout bite of the vaginal wall adjacent to the urethra. This change should avoid the risk of urethral damage. Although hematuria and the formation of a fistula were never problems complicating the initial series of cases, eliminating the hazard of injury to the urethra by placing the sutures solely in the vaginal wall should lend more security to their grasp. Instead of allowing the Foley catheter to remain in the bladder for several days, it is now removed immediately after operation. On seven more recent occasions, the suprapubic wound was closed without drainage.

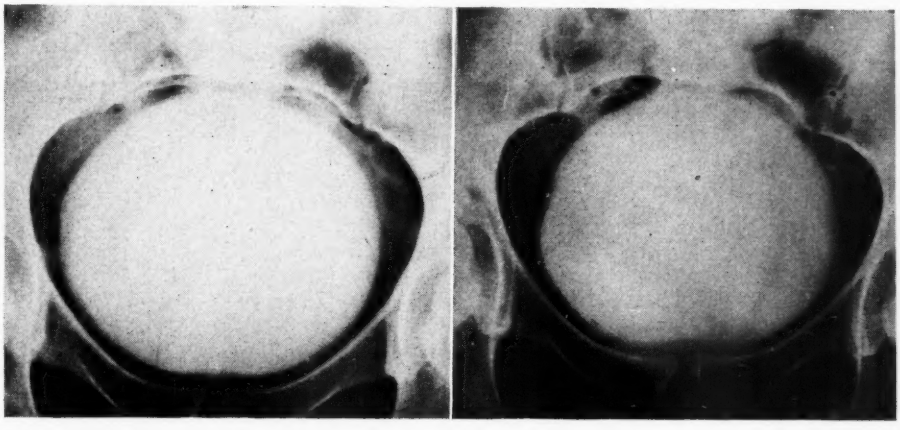
As part of the study, cystometry and cystography before and after operation were used as additional sources of information.

The cystometric determinations showed a comparably normal detrusor mechanism in every instance. No change was noted that could be associated solely with stress incontinence or the correction of it. The importance and usefulness of cystometry in the differential diagnosis of conditions causing increased intravesical pressure or a neurogenic bladder are appreciated.

The cystogram was the source of more positive information. A total of seventy-five cystographic observations were made on eight of the patients with incontinence and on five continent women used as controls. From 200 to 250 c.c. of 5 per cent sodium iodide were instilled into the bladder for cystography. Films were taken before and after operation with the patients in the recumbent and erect positions, and also while voiding in the standing position.

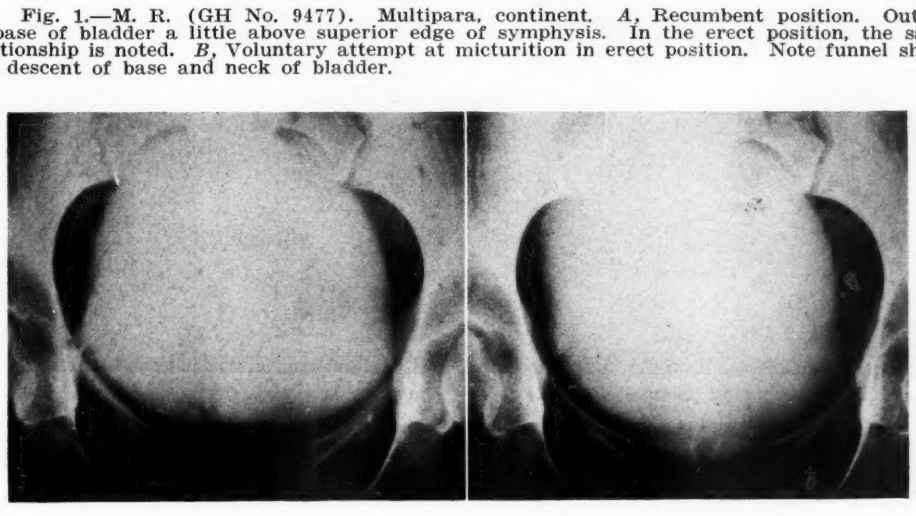
In the continent woman while she is recumbent, the outline of the base of the bladder lies just at or little above the symphysis pubis (Fig. 1, *A*). When she stands erect, the position of the bladder is maintained (Fig. 2, *A*). A voluntary attempt at micturition transforms the base of the bladder to a funnel-

shaped structure and shows some descent of the vesical neck (Fig. 1, *B*). As micturition is initiated, the effect of the detrusor mechanism is noted in the change of the shape of the bladder and in the "funneling" and descent of the vesical neck (Fig. 2, *B*). It should be stated that the subjects used as controls were nulliparous and parous women with normal urinary control and well-supported vaginas.



A. *B.*

Fig. 1.—M. R. (GH No. 9477). Multipara, continent. *A*, Recumbent position. Outline of base of bladder a little above superior edge of symphysis. In the erect position, the same relationship is noted. *B*, Voluntary attempt at micturition in erect position. Note funnel shape and descent of base and neck of bladder.



A. *B.*

Fig. 2.—E. E. (GH No. 6146). Nullipara, continent. *A*, Erect position. Level of base of bladder just above symphysis. Same relationship observed with patient in recumbent position. *B*, Act of micturition initiated. Note funnel shape and descent of base and neck of bladder.

In seven of the patients with stress incontinence, the findings as revealed by cystography before operation were essentially uniform. In the recumbent position, the base of the bladder is well below the superior border of the symphysis (Figs. 3, *A* and 4, *A*). In the erect position, the bladder descends a little lower with the base and neck assuming the shape of a funnel (Figs. 3, *B* and 4, *B*). These observations indicate that there must be some weakness or relaxation predominantly of the supportive structures of the pelvic floor, or of the internal vesical sphincter mechanism, or both.

The exception to these regular findings was noted in the eighth patient with stress incontinence of moderate degree and without any clinical evidence of loss of vaginal support. Both in the recumbent and standing positions, the cystograms failed to demonstrate the characteristic shadows of the incontinent bladder, in fact, they were not unlike those of the continent woman (Figs. 5, *A* and 5, *B*). This situation, in the absence of other demonstrable causes, points to an incompetent vesical sphincter not associated with inadequate vaginal support.

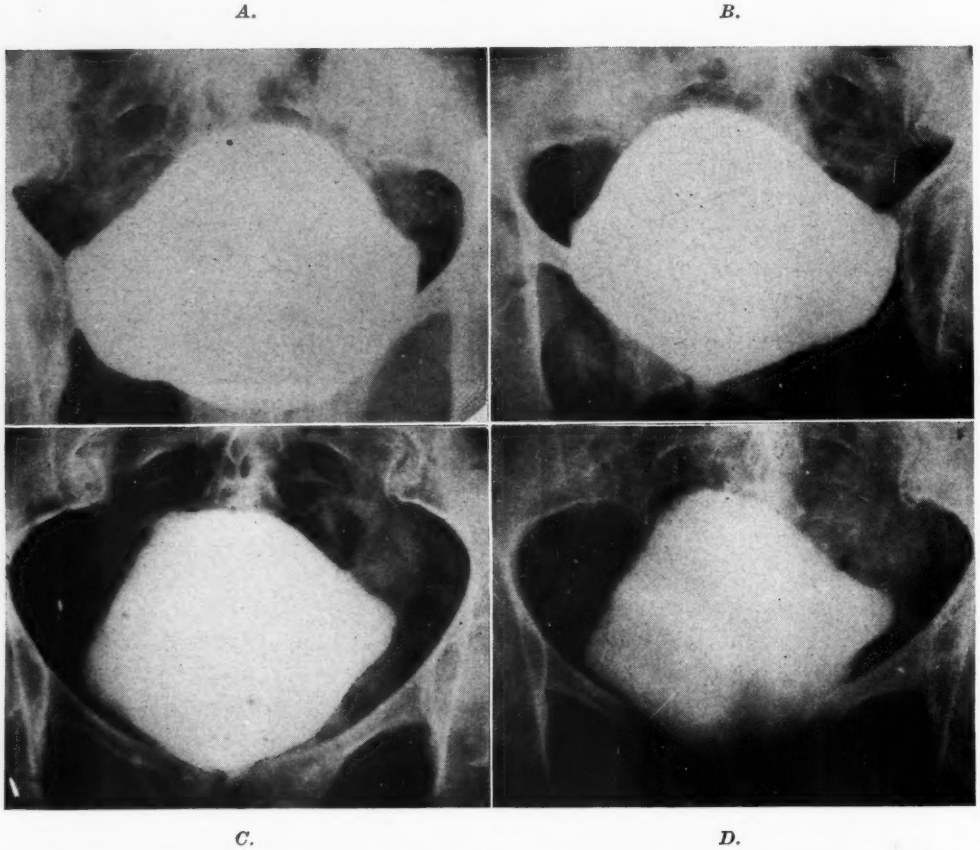


Fig. 3.—C. Y. (GH No. 16755), aged 51 years. Nullipara, stress incontinence with moderate urethrocystocele. *A*, Recumbent position before operation. Base and neck of bladder well below superior border of symphysis. *B*, Erect position before operation. Note descent and "funneling" of vesical outlet. *C*, Recumbent position after operation. *D*, Erect position after operation. Note degree of elevation of bladder.

In general, these observations on the continent and incontinent bladder are in agreement with those just recently published by Muellner.[3] His study on the etiology of stress incontinence based on many fluoroscopic observations not only comprises illustrations of the position of the bladder and vesical neck in subjects who have normal urinary control and in those who are incontinent, but also demonstrates the mechanics of micturition in both.

Following suprapubic vesicourethral suspension, the most striking observation made by cystography is the degree of elevation of the bladder that is effected by the operations (Figs. 3, *C*, 3, *D*, 3, *E*, 4, *C*, 4, *D*, 5, *C*, 5, *D* and 5, *E*). Although urinary control has been restored in all of these patients to date, it is noted that the position of the base of the bladder is slightly lower in the erect posture when compared to the recumbent (compare Figs. 3, *C*, 4, *C*, 5, *C* to

Figs. 3, *D*, 4, *D*, 5, *D*). Some of the distortion that is noted of the vesical shadows postoperatively are inevitably the result of the manner in which the structures were fixed to the symphysis and the adjacent tissues. It is observed that the bladder neck and the urethra are closely approximated to the superior surface of the symphysis pubis without showing any distortion of their contour and lumen (Fig. 6).

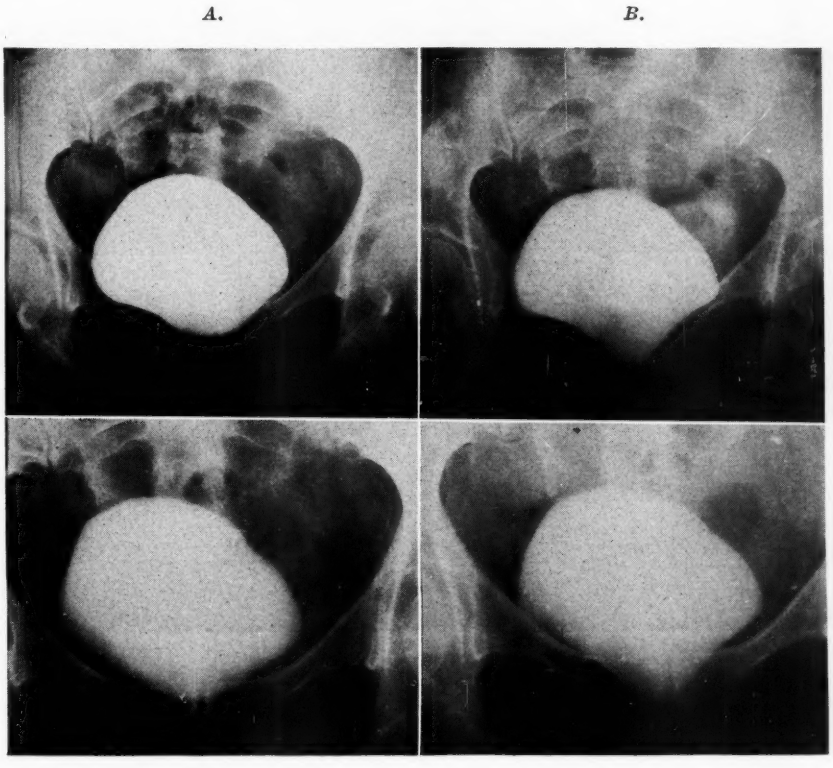
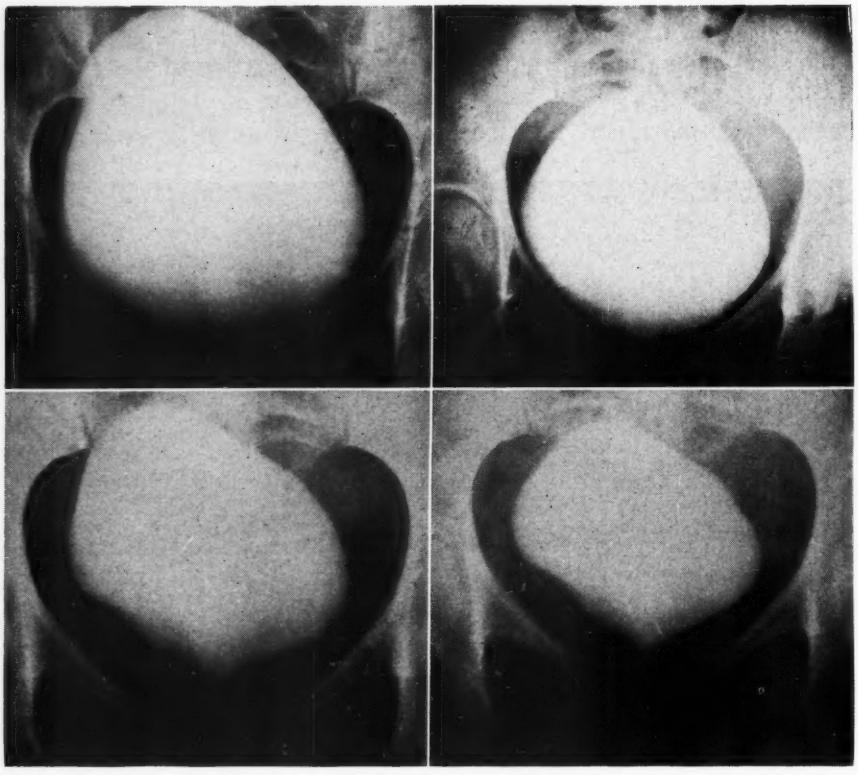


Fig. 4.—E. C. (GH No. 12662), aged 60 years, para iii. Recurring stress incontinence after Manchester type of repair and plication of vesical sphincter. *A*, Recumbent position. *B*, Erect position before operation. Level of base and neck of bladder well below superior border of symphysis. *C*, Recumbent position. *D*, Erect position after operation. Note degree of elevation.

Two clinical histories should be briefly reviewed at this point. First, the case that required a second vesicourethral suspension.

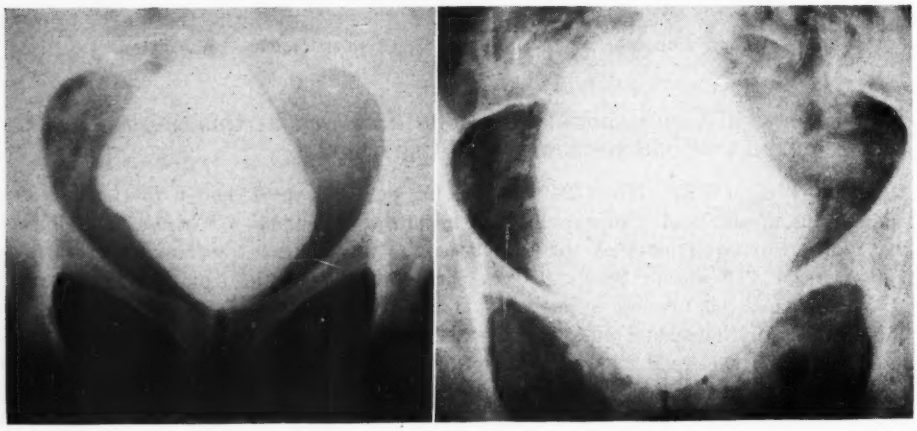
CASE 1.—T. L. (WRH, No. 279499), para iii, aged 39 years, had a total hysterectomy for a submucous myoma and a suprapubic vesicourethral suspension for stress incontinence on July 29, 1948. During October of the same year the incontinence recurred and became progressively worse. The author was called in consultation early in April of this year. By vaginal examination the urethra appeared to be well suspended. Stress incontinence, however, could be readily demonstrated. The preoperative test indicated that she was eligible for a second operation. On April 22, 1949, the author personally explored the site of the former operation and it was found that most of the urethra was well fixed and densely adherent to the posterior surface of the symphysis, but that the vesical neck and base of the bladder were relaxed and unsupported. The suspension and fixation of these structures were accomplished accordingly. The patient was discharged from the hospital in due time with a satisfactory recovery.



A. *B.*

C. *D.*

Fig. 5.—E. H. (GH No. 17692). aged 44 years, para iv. Stress incontinence without any clinical evidence of lose of support. *A*, Recumbent position. *B*, Erect position before operation. Note lack of descent of bladder. Findings simulate those observed in normally continent woman. *C*, Recumbent position. *D*, Erect position after operation. Degree of elevation of bladder is notable.



3*E*. 5*E*.

Figs. 3*E* and 5*E*.—Position of bladder during micturition after operation.

It was revealed by the former operator, who was attempting the procedure for the first time when he did the operation in July, 1948, that he had employed only six sutures to fix the urethra to the symphysis, and had failed to suspend the vesical outlet and base. If in this patient's follow-up she remains continent, the reason for the failure following the first operation is obvious.

Fig. 6.—B. B. (GH No. 8482), aged 34 years. After operation for stress incontinence. Half lateral view showing close approximation of urethra to posterior surface of symphysis. No distortion of urethra is in evidence.

The second case came under observation at the Gallinger Municipal Hospital.

CASE 2.—F. W. (GMH No. D271), para viii, aged 36 years, was admitted Aug. 8, 1948, complaining of urinary stress incontinence. She had a second-degree urethrocystocele. Her last menstrual period began July 13, 1948. A suprapubic vesicourethral suspension was performed on August 12. No menstrual period appeared in August and shortly thereafter the diagnosis of pregnancy was established. Throughout pregnancy good urinary control was maintained. The disposition of the case when she would reach term was repeatedly discussed and cesarean section was considered. On March 3, 1949, approximately six weeks before the estimated date of confinement, she was admitted to the delivery suite with ruptured membranes, the vertex deeply engaged, and after a labor of two hours and fifteen minutes with the aid of a midline episiotomy was delivered spontaneously of an infant weighing 5 pounds, 5 ounces. To date she has retained good urinary control.

This case is unique in the sense that it is the first record of a pregnancy and delivery, albeit premature, occurring soon after this type of operation. It raises the question whether cesarean section will be found necessary under such circumstances, inasmuch as the location where the defect is corrected is at the outer periphery of the birth canal and fixed to a position where trauma from overstretching is less likely.

Comment

However controversial are the reasons advanced to explain the causes of female urinary stress incontinence, it seems fairly established that the strategic factor in the restoration of urinary control lies in the rehabilitation of the vesical sphincter mechanism located in the bladder neck and the upper third of the urethra. Failure of the pelvic floor, especially the levator ani, to support the vesical neck, weakness or relaxation of the internal sphincter mechanism

of the urethra, any separation of the normal anatomical attachments of the vesical sphincter mechanism may result in stress incontinence. Whether these defects are caused by trauma associated with childbirth and obstetrical procedures, by congenital weakness, or by changes associated with senility, it is the vesical sphincter mechanism that occupies the center of the stage. Kelly[4] aptly states that "the key to successful treatment lies at the internal orifice of the urethra and in the sphincter muscle which controls the canal at this point." The case that required a second vesicourethral suspension adequately illustrates why the first one might have failed. The key to successful treatment, that is to say, the importance that should have been given to the elevation and fixation of the bladder neck, was overlooked.

It is known that stress incontinence may develop in the absence of any clinical evidence of the loss of the supporting structures in the pelvic floor, just as it is known that urinary control may be maintained in the presence of some relaxation. An evaluation of the cystographic findings that were observed in this study gives evidence that relaxation of the structures supporting the bladder neck is most frequently associated with stress incontinence.

Without excluding the usefulness and the indications of other operations that have long been tried and found successful, further evaluation of the experience that has been gained from the use of suprapubic vesicourethral suspension for the correction of stress incontinence presents the following points of advantage. The approach is simple and the technique is not difficult. The field of operation is relatively roomy and permits of a full view of the superior and lateral aspects of the urethra, the all-important neck of the bladder, and the base of the bladder. The procedure may follow a laparotomy in cases where combined vaginal surgery may not be indicated, but the need for the correction of exertional incontinence is present. It may be elected among elderly patients in whom a major vaginal operation is not advisable, but the restoration of urinary control is paramount for their comfort and well-being. It may be further elected in women, particularly those in the childbearing age, who complain solely of stress incontinence and who appear to have no need for vaginal plastic surgery. It is especially an advantageous procedure in cases of recurring loss of urinary control where repeated standard vaginal operations have failed.

The postoperative cystographic observations demonstrate that the most evident change effected by the procedure is the elevation of the bladder and the vesical outlet, and the fixation of the urethra without distorting it to the posterior surface of the symphysis pubis.

Since no muscles are plicated and no hammocklike support is constructed under the internal sphincter, it appears that the mechanism by which simple vesicourethral suspension restores or improves urinary control is as it was implied in the analysis of the original series. Most sphincters have two or more relatively firm attachments for the execution of their normal function. Simple elevation and fixation of the vesical outlet and urethra provide such attachment, and are a major factor in the maintenance of urinary control.

Summary

The selection of twelve patients with urinary stress incontinence forms the basis of this study. Simple vesicourethral suspension as described by Marshall and his co-workers was the procedure used to correct their complaint. An evaluation of the clinical and anatomical findings observed before correction, particularly with the aid of cystography, showed that failure of the pelvic floor, especially of the levator ani, to support the vesical sphincter mechanism

was most frequently associated with loss of urinary control. Cystography postoperatively revealed the striking degree of elevation of the bladder and its outlet effected by the operation. It further demonstrated that the procedure fixes the urethra to the posterior surface of the symphysis without distortion. Although suprapubic vesicourethral suspension is not meant to supplant the standard vaginal operations for the relief of stress incontinence, some of the advantages are enumerated. It is indicated, as a result of this study, that the mechanism of the operation's success lies in the fact that it restores a relatively firm point of attachment to the sphincter mechanism of the vesical neck, a major requirement for the normal function of any sphincter.

References

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2. Shaw, W.: Surg., Gynec. & Obst. **88**: 11-22, 1949.
3. Muellner, S. R.: Surg., Gynec. & Obst. **88**: 237-242, 1949.
4. Kelly, H. A.: Urol. & Cutan. Rev. **17**: 291, 1913.

Discussion

DR. JAMES R. MILLER, Hartford, Conn.—A short time ago I reported at this Society this same operation, devised by Hepburn for the correction of prolapse of the urethra, and I made it plain that we were not speaking of the incomplete and partial prolapse but of the real one, where the urethra turns itself inside-out. The first patient I had was seventy years old and, as Dr. Marchetti has said, the procedure is extremely simple. Following operation this patient voided without difficulty and without a catheter. About six months later I did a LeForte operation.

I would commend this surgical procedure for consideration. The exposure is excellent. I have never done it for stress incontinence but have used it in five patients with prolapse of the urethra.

DR. T. C. PEIGHTAL, New York, N. Y.—Dr. Marchetti has described to us what may well be one of the most important contributions to the operative attack on that often perplexing problem of stress incontinence. Most of us are familiar with his report recently published conjointly with Drs. Marshall and Krantz, giving the technique of this vesicourethral suspension operation, the preliminary test essential to selecting candidates for this procedure, and the end results in thirty-eight cases. The 8 per cent of failures in this first group may well be attributed to the vagaries of developing a new operative procedure.

The additional study of twelve cases in which this operation was carried out personally by the author forms the basis of today's report. These cases comprise varied examples of stress incontinence in middle-aged and elderly patients, in nulliparas and multiparas, in many of whom other operations for relief of this troublesome symptom had failed.

The alteration in the technique of placing the periurethral sutures, namely, in the vaginal wall only, rather than including the urethral wall as described in his original article, is a distinct improvement and in the hands of various operators will help to prevent urethral injury. The necessity of placing supportive sutures in the bladder neck and lower bladder wall to the upper posterior symphysis or lower abdominal wall fascia is properly stressed.

The removal of the indwelling Foley catheter at the end of the operation we hesitate to endorse without trial, since most of these cases have some hematuria for forty-eight hours and it seems to us that retention of the Foley catheter over this period is desirable so that small clots, if present, may be washed out by frequent irrigation. How-

ever, we agree that the catheter should be removed as early as possible since these patients void promptly and, for the most part, have no residual urine. Since this operation results in a very dry field, drainage through the wound of the space of Retzius is seldom necessary or desirable.

By his cystographic studies Dr. Marchetti has shown convincingly both the anatomic bladder defect in stress incontinence and how his operation overcomes this defect. His theorizing on the injury to and the repair of the supports necessary to proper function of the vesical sphincter mechanism is sound.

A preliminary report of the Marshall-Marchetti pin-up operation, by which name this vesicourethral suspension has come to be designated in New York, was given at the New York Obstetrical Society in May, 1948. It came to me personally at a time when I was dissatisfied over the number of essentially poor results we were obtaining on our service with the Kennedy type of fascial plication repair for stress incontinence which we have used for some years, and when the use of urethral supporting fascial strip from the abdominal wall, while for the most part successful in our clinic, were resulting in too many complications, such as overcorrection, failure of strips to hold, and one or two instances of urethral damage. Therefore, the possibilities of the procedure which Dr. Marchetti has described seemed most acceptable: its technical simplicity, its lack of risk, particularly in elderly patients where length of operative time is important, its fresh field of approach through the space of Retzius rather than through the multiple scars of former vaginal operations, and its reported high degree of success with a minimum of complications, convinced us to give it a try.

Accordingly, since last August we have done the operation on five patients in all of whom one or two previous vaginal operations for stress incontinence had been performed with poor results, there in our own clinic. Their ages were 41, 53, 60, 69, and 74 years. One was nulliparous, one para ii, and three para iii. Leakage had been noted from one to ten years. As to results, four have been wholly satisfactory and one (our second attempt at this procedure) was a complete failure due to the breaking away of our suture supports from the coughing of postoperative atelectasis. Since this experience we have placed packing in the vagina as a splinting support for forty-eight hours. However, this is probably an unnecessary precaution in most cases.

Our experience has convinced us that Dr. Marchetti and Dr. Marshall have devised an operation for stress incontinence which is not time consuming, which is easy of execution, which can be combined with both other abdominal and vaginal procedures, which is particularly adaptable and effective in cases where other measures by the vaginal route have failed, and which promises to give results far superior to any fascial strip transplant procedures which have been devised to date.

DR. R. GORDON DOUGLAS, New York, N. Y.—Last week the ninetieth operation according to the technique described by Dr. Marchetti and Dr. Marshall was performed in our Hospital (New York Lying-In). The results have been satisfactory in 87 per cent of the patients, although in many instances the period of follow-up is not long.

I have one suggestion to make in respect to Dr. Marchetti's cystographic studies; viz., that a true lateral cystourethrogram better demonstrates the position of the bladder neck than an anteroposterior plate. In our clinic, we have completed research by means of a true lateral cystourethrogram utilizing a modified Foley catheter filled with 30 per cent sodium iodide for contrast. The bladder neck can thus be marked in relation to the symphysis in the standing and sitting positions and while the patient is at rest or attempting to void. This method has been useful to us particularly in studying the recurrent cases. It has another practical application in that it guides the operator in correcting the anatomical displacement of the bladder neck and urethra.

DR. MARCHETTI (Closing).—I failed to mention that our cystographic findings before operation, in general, are in agreement with those recently published by Muellner.

I appreciate Dr. Douglas's suggestions. We are planning to do a study on urethral visualization by using opaque substances.

LIGATION OF THE VENA CAVA AND OVARIAN VESSELS*

A Follow-Up Study of 59 Cases

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THE dramatic response obtained in a patient with acute suppurative pelvic thrombophlebitis by ligation of the inferior vena cava and ovarian vessels performed Feb. 2, 1942, by one of us (C. G. C.) led to treatment by this procedure of other patients failing to respond to a medical regimen. The results obtained in our earlier cases were reported in May, 1942.[1, 2] Subsequent communications[3, 4] have appeared as the series has increased. To date, fifty-nine consecutive patients with ligation of the vena cava and ovarian vessels have been observed. The youngest patient was 15 years old and the oldest was 65 years old. Six of the operations in the series were performed by members of the Department of Gynecology and Obstetrics of the Louisiana State University School of Medicine, and fifty-three by members of the Departments of Gynecology and Obstetrics of Tulane University School of Medicine. With the exception of two patients, all were supervised preoperatively, at operation, and postoperatively by one or all of us. Most of the patients were under the direction of the senior author. Forty-six patients were treated at Charity Hospital of Louisiana in New Orleans, and thirteen at various private institutions. Repeated follow-up observations of these patients by us and detailed studies of the vascular status of the extremities by Drs. Ray, Burch, Winsor, and their associates in the Department of Medicine, Tulane Medical School, form the basis of this report. Twenty-seven of the patients have been followed from two to seven years and twenty-five less than a year (Table I).

TABLE I. YEARS FOLLOWED IN 52 CASES

YEARS FOLLOWED	NO. CASES
0-1	25
1-2	7
2-3	7
3-4	6
4-5	2
5-6	0
6-7	5

*Presented at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

It is to be emphasized that ligation was performed on patients only if they failed to respond to the medical therapy popularly employed at that time. Patients admitted with pulmonary infarction constituted the sole exception in that they were immediately subjected to ligation. When sulfonamides, penicillin, and streptomycin became available, they were used in accepted dosage. During the past year, these preparations have been given in combination. In a few patients dicumarol, heparin, or a combination of the two, was also given. Thus, operation was performed on those critically ill patients with the most severe inflammatory processes who proved to be resistant to all other therapy.

Indications

The high mortality rate associated with nonoperative therapy in suppurative pelvic thrombophlebitis prior to 1942, the futility of ligation of the ovarian vessels alone or in combination with one or more of the major pelvic veins, and the good results obtained in our earlier cases in which the normal venous return from the uterus was interrupted, i.e., ligation of the vena cava and ovarian vessels, led in June, 1942, to a formulation of indications for ligation. It was hoped that, with the advent of many chemotherapeutic and antibiotic agents, this suppurative process might be controlled, but this has not been found to be true in all cases. Furthermore, neither the anticoagulants, nor a combination of anticoagulants, chemotherapeutic agents, and antibiotics have produced recovery in all cases.

It is our opinion today as in 1942 that ligation of the vena cava and ovarian veins is indicated in the following cases:

1. Patients with suppurative pelvic thrombophlebitis who fail to improve after four or five days of medical regimen (blood, chemotherapy, antibiotics).
2. Patients with suppurative pelvic thrombophlebitis, receiving nonsurgical treatment, in whom pulmonary infarction develops irrespective of the duration of medical regimen.
3. Patients with suppurative pelvic thrombophlebitis and evidence of infarction on admission. Operation is performed on these patients *immediately*.
4. Patients with large pelvic tumors complicated by phlebothrombosis, thrombophlebitis, or both, involving the iliac vessels.

Surgical Approach

In cases of suppurative pelvic thrombophlebitis following abortion, delivery, irradiation, or complicating pelvic abscesses the transperitoneal approach is employed, since a successful result in these cases depends upon ligation of the normal venous return from the uterus, and by the transperitoneal approach both ovarian vessels and the vena cava can be inspected and ligated. In patients with suppurative pelvic thrombophlebitis following hysterectomy, the vena cava may be ligated extraperitoneally, as the continuity of the ovarian vessels with the pelvic veins has already been interrupted at the time of hysterectomy. The same approach is indicated in cases of phlebothrombosis involving the common femoral vein or veins (or higher) in both sexes.

Case Mortality Rate

Of the 59 patients, 52 survived (88 per cent) and 7 died (12 per cent) (Table II). The diagnosis of suppurative pelvic thrombophlebitis was substantiated at operation or autopsy in all the patients who died. All patients who died within one year of operation were considered operative failures, since it is our belief that nothing was accomplished if the patient died of dis-

tant metastasis even though the vena cava and ovarian vessels were successfully ligated. It is important to note that the highest case mortality rate occurred in 1946 (Fig. 1), when penicillin became available to us. In an attempt to evaluate accurately its use in suppurative pelvic thrombophlebitis, operation was delayed in two cases longer than our surgical judgment deemed advisable. In fact, four of the seven patients who died were operated on from nine to twenty-one days following admission to the hospital. In our experience, if chemotherapy and antibiotics are to produce results, great improvement will be noted within four to five days following their administration.

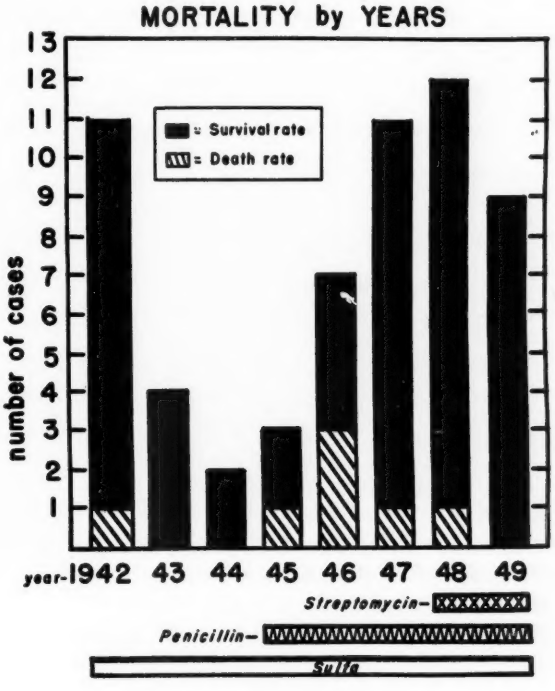

Fig. 1.

TABLE II. CASE MORTALITY RATE (UNCORRECTED)

PATHOLOGIC PROCESS	CASE	LIVED	DIED
I. *Suppurative Pelvic Thrombophlebitis.*—			
1. Acute			
(a) Puerperal	48	42	6
(b) Posthysterectomy	5	5	0
(c) Postradiation	1	1	0
(d) Perirectal abscess	1	0	1
(e) Posttraumatic	1	1	0
2. Chronic	1	1	0
II. *Phlebothrombosis Complicating Uterine Fibroids*	2	2	0
Total	59 (100%)	52 (88%)	7 (12%)

In only one case might the procedure itself have been responsible for death, as this patient died immediately following operation (Table III). However, the pathologic condition noted at operation and autopsy makes this questionable. Although ligation of the vena cava upon a critically ill patient has been considered by some[5] to result in a high mortality rate, this has not

been our experience. The critically ill patient is the one who most needs it. Most of the deaths in this series were caused not by the operation itself but by *delay* in operating.

TABLE III. DEATHS

PATIENT	ADMITTED	OPERATED UPON	DIED	CAUSE OF DEATH
H. A.	4/15/42	4/18/42	4/18/42	Peritonitis, pulmonary infarct, splenic infarct, postabortal pyometra, thrombus which involved superior vena cava and auricle of heart, postabortal (autopsy)
A. B.	3/15/42	3/20/46	6/28/46	Ruptured mycotic aneurysm, inferior mesenteric artery, acute bacterial endocarditis superimposed on old rheumatic valvulitis, postabortal (autopsy)
E. F.	6/ 8/46	6/21/46	7/14/46	Subacute bacterial endocarditis, postabortal (clinical)
M. T.	1/ 4/45	1/25/45	1/30/45	Septicemia, postabortal (clinical)
G. C.	12/16/47	12/18/47	12/23/47	Septicemia *(Staphylococcus aureus)*, postabortal (clinical)
F. S.	9/30/48	10/ 9/48	11/17/48	Possible lupus erythematosus, fibrinous pericarditis, granular vegetations of mitral valve, retained secundines, postabortal (autopsy)
M. A.	8/30/46	9/11/46	9/20/46	Uremia, pyelonephritis, pleural effusion, bronchopneumonia, pulmonary tuberculosis caseous right lobe, perirectal abscess, infarct of spleen (massive hemorrhage from abscess wall) (autopsy)

Three patients died of unrelated conditions, two, three, and two years, respectively, after operation. As can be seen in Table IV, in no way could death be attributed to complications of the procedure. Until the time of death all had normal menstrual function, exhibited no evidence of edema or ulceration of the extremities, and led a normal active life.

TABLE IV. LATE DEATHS

PATIENT	OPERATION	DEATH	CAUSE OF DEATH
O. D.	1942	1944	Arsenical encephalopathy
G. L.	1942	1945	Third degree burns of body
J. D.	1942	1944	Hemorrhage at time of lobectomy

Condition of Lower Extremities

The channels involved in the passage of blood from the pelvis and lower extremities following ligation of the inferior vena cava have been repeatedly studied. Recently, Robinson,[6] from an excellent review of the literature on this subject as well as from his own experimental work, concluded that the vertebral, azygos, and portal systems of veins are the most important routes of collateral circulation and the superficial veins of the trunk are the least important. Infrared photographic studies by us substantiate the latter statement (Figs. 2 and 3).

Immediately following ligation of the inferior vena cava, mild edema of the leg and ankle is noted in most cases, but it usually disappears completely within a few weeks or months. Retrograde thrombi occasionally develop but respond readily to lumbar sympathetic block. In nearly all of our patients the right or left lumbar sympathetic chains, or both, were severed at the time of ligation, or lumbar sympathetic blocks were performed postoperatively on the uninterrupted side or sides. We believe that such procedures are valuable adjuncts in relieving

the arterial spasm occasioned by ligation of a large venous trunk and that the absence of postoperative complications in the legs is in no small part due to these precautionary measures. Pronounced edema of the extremities followed ligation of the vena cava and ovarian vessels in a few patients; this usually occurred in those patients in whom retrograde thrombi developed or in those who had had previous evidence of intravascular clotting in the venous drainage from the lower extremity prior to caval ligation. To date, nine patients still have edema, which is mild in all except one patient, who had recurrent phlebitis and edema of eleven years' duration. On Dec. 9, 1946, lumbar sympathectomy was performed in an attempt to reduce the swelling, and unbridling of the left common femoral vein was done in March, 1947. On May 8, 1947, the inferior vena cava was ligated. Since then, the phlebitis has not recurred and the patient's condition is much better than before ligation, though edema persists and is greater than in any of our other patients (Fig. 4, *B*).

A. *B.* *C.*

Fig. 2.—Infrared photographic study of veins of abdominal wall. *A*, Case M. H., normal term pregnancy. *B*, Control, no history of vascular disease. *C*, Case J. D., post-caval ligation, three months.

In two patients ulceration developed over both internal malleoli. In one patient severe varicosities were present for years prior to operation, and discoloration and edema were evident preoperatively about the malleoli. The vena cava and ovarian vessels were ligated July 9, 1947, but the patient failed to wear elastic stockings or ace bandages on returning home. She was again seen in January, 1949, when the ulceration was detected. She was given elastic stockings to wear and the ulcers are healing (Fig. 4, *A*). However, all this time she has performed all her household duties for a family of seven. The other patients in whom ulceration developed had the severest preoperative thrombophlebitis of the leg and pelvic veins that we have encountered. Following ligation of the vena cava a retrograde thrombus developed on the opposite side but edema in the involved leg subsided rapidly. Two years after ligation ulcerations developed over both medial malleoli. Wearing elastic stockings resulted in complete healing within a few weeks. This patient is the wife of a farmer and has not been incapacitated in the performance of her routine household and farming duties.

In four patients operation was performed during the past three months and edema of the ankles is noted in the evenings after the patients have been up and about all day. Each month brings less edema and it is highly probable that these patients will be entirely free of symptoms within a month or two, as have the others in the series who had mild edema following operation. In two other patients operated on for femoral and suppurtaive pelvic thrombophlebitis, mild edema of the ankles is noted in the late evening but there is no limitation of activity. All except one patient wear the same type and size of shoe that they wore prior to operation.

A. *B.* *C.*

Fig. 3.—Infrared photographic study of veins of extremities. *A*, Case A. L., varicosities and post-caval ligation (two years). *B*, Control, no history of vascular disease. *C*, Case J. D., post-caval ligation, three months.

A. *B.* *C.*

Fig. 4.—Edema and ulceration. *A*, Case A. L., varicosities, post-caval ligation (two years), ulceration over both medial malleoli. Only two patients in the series had ulcerations. *B*, thrombophlebitis of leg of eleven years' duration; sympathectomy, unbridling left femoral vein; post-caval ligation (two years); this was the only patient in the series showing this degree of edema. *C*, post-caval ligation (two years); this is a typical result.

Evaluation of Vascular Status

Certain physiologic observations made in the Tulane Department of Medicine revealed some interesting findings. The venous pressures in the veins of the lower extremities varied from low normal values (120 mm. of water pressure) to exceedingly high values (over 600 mm. water). In the initial determinations few fell within the limits of normal. In the same patients there were differences in the pressures in the two sides (Fig. 5). With time there is a decline in pressures toward normal and in a number of instances to within normal limits (Fig. 6).

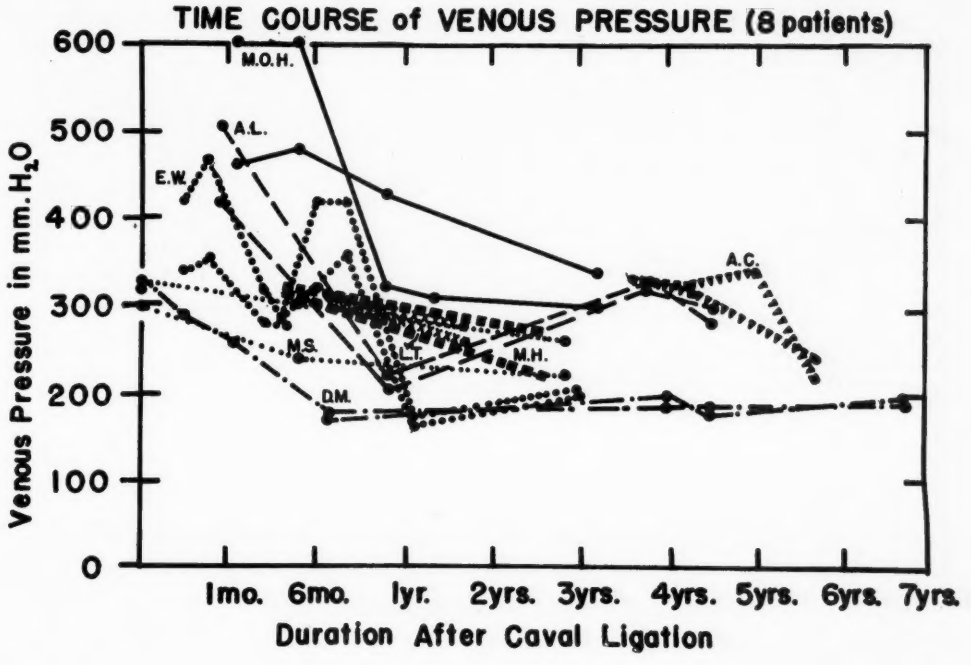

Fig. 5.

As stated previously, edema of the lower extremities is usually present immediately after operation, but it does not always occur. The degree of edema varied from a trace to 4 plus, but in all instances has not persisted beyond the sixth month after operation, and in most of the patients edema completely subsided by the sixth week. The degree of edema was not related to the venous pressures (Fig. 7). In some, edema was pronounced with moderate or relatively low pressures; in others with notably high venous pressures there was no edema. In some the edema which was present initially disappeared without a change in venous pressure. From these observations one can conclude that although venous pressure plays a role in the development of edema, it is not the sole or major factor.

Tissue pressure increases and venous pressure increases were concomitant observations. This would tend to decrease the formation of edema. Plethysmographic studies of the toes revealed pulsations which were somewhat reduced but within the limits of normal. Sympathetic section increased the pulse deflections.[7] Measurements of circulation time from foot to heart, by means of a radioactive isotope, revealed variable durations but all were within normal limits.

These observations, although not clearly defining all the circulatory adjustments, do indicate that there is adequate compensation for vena cava ligation.

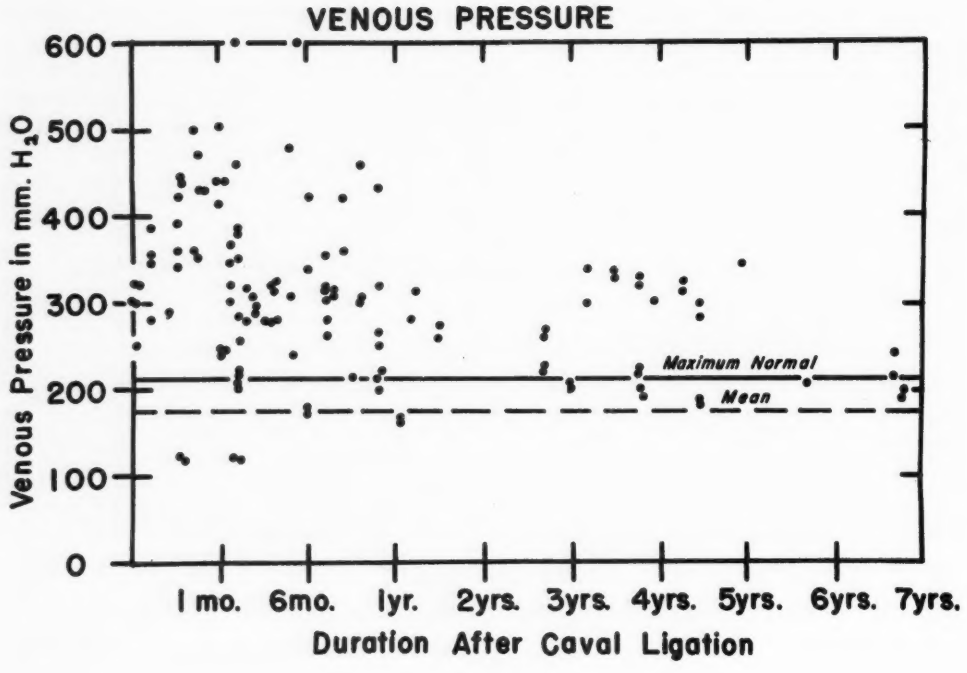
VENOUS PRESSURE
600
500
400
300
200
100
0
Venous Pressure in mm. H_2O
Maximum Normal
Mean
1 mo.
6mo.
1yr.
2yrs.
3yrs.
4yrs.
5yrs.
6yrs.
7yrs.
Duration After Caval Ligation

Fig. 6.

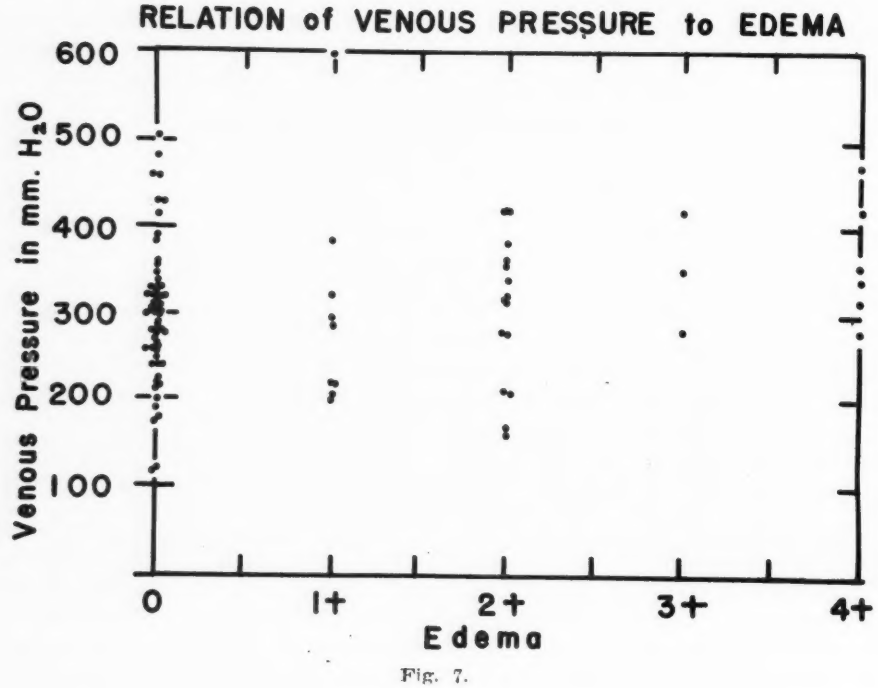
RELATION of VENOUS PRESSURE to EDEMA
600
500
400
300
200
100
Venous Pressure in mm. H_2O
0
1+
2+
3+
4+
Edema

Fig. 7.

Fertility and Ovulation

No detailed effort has been made to determine the effect on fertility in all patients subjected to ligation of the inferior vena cava and ovarian vessels. From the beginning it was assumed that the inflammatory nature of the disease would render the majority of patients sterile or relatively infertile. However, the occurrence of a few pregnancies subsequent to ligation prompted a brief inquiry into the fertility status of these patients.

Of the 59 patients operated upon, 7 died in the hospital, and 16 had sterilizing operations, leaving 36 in whom pregnancy was anatomically possible. Age (fifth decade or over) eliminated three others, and three patients died within three years of operation, so that there were 30 patients in whom conception was theoretically possible.

These patients have not been questioned regarding the desire for pregnancy, attempts at conception, use of contraceptives, or health of the husband. However, the fact that the majority of operations was necessitated by postaboral sepsis indicates a lack of enthusiasm for childbearing. Nevertheless, six pregnancies have occurred to date among five patients, and of these pregnancies four proceeded to term. All term pregnancies ran a normal prenatal course without complications. Embarrassment of the general circulation, dependent edema, leg cramps, varicosities, or other evidence of inadequacy of the collateral circulation did not occur. One patient required cesarean section because of contraction of the pelvis and previous section, but the other three labors were entirely normal, as was the puerperium in all patients. One woman had a miscarriage at four months, and in another criminal abortion was performed at six weeks.

Of the twenty-five remaining patients who have not had a known conception, nine were operated on less than four months ago. This leaves sixteen patients in whom fertility should be investigated. Without fertility surveys in these patients we can only speculate as to how many were really desirous of pregnancy, how many have been rendered sterile by their disease, and how many have suffered reduced fertility because of the operation.

Basal temperature records were considered to be too intricate for the majority of these patients. Among the surviving thirty patients in the reproductive age, five exhibited ovulation by pregnancy. Fifteen of the remainder had endometrial biopsies performed, ten of whom exhibited progestational endometrium, and five estrogenic. Thus, fifteen of the thirty afforded evidence of ovulation, either by pregnancy or endometrial pattern. Eleven patients were not studied from this standpoint (nine were too recently operated upon), and five patients showed an endometrial pattern inconsistent with ovulation. Among these latter five, two were operated on less than three months ago, and in one patient a corpus luteum was demonstrable at exploratory laparotomy.

These observations would suggest that ligation of the ovarian vessels (arteries and veins) and inferior vena cava does not seriously interfere with ovulatory function in the majority of patients.

Additional Surgical Procedures at the Time of Ligation

Ligation of the vena cava is a relatively simple procedure which is not accompanied by any great degree of shock. As stated before, in many patients the right or left lumbar sympathetic chain, or both, was sectioned at the time of ligation. In a few, unilateral salpingo-oophorectomy for severe thrombosis and infection involving the ovary was necessary. In one patient bilateral salpingo-oophorectomy was performed, as both ovaries were cystic. In four patients hysterectomy was done at the same time, either as a planned procedure or necessitated by the pathologic condition encountered (Table V). In another patient nephrectomy was necessitated by an ectopic kidney on the right side with

the thrombosis extending into the renal vein. There were no deaths and the morbidity was not increased in this group. Since then there has been no activity of the phlebitic process.

TABLE V. HYSTERECTOMY AT TIME OF VENA CAVA LIGATION

PATIENT	OPERATION	PATHOLOGY
M. A.	5/25/46	Acute suppurative pelvic thrombophlebitis; partially retained placenta
A. D.	12/10/48	Chronic suppurative pelvic thrombophlebitis; dyspareunia, severe; badly lacerated cervix with severe endocervicitis
E. W.	2/ 5/46	Acute suppurative pelvic thrombophlebitis; uterine fibroids
H. W.	12/31/48	Acute suppurative pelvic thrombophlebitis; gangrene of uterus

Subsequent Surgical Procedures

Twelve patients have undergone some surgical procedure since ligation of the vena cava. The dates of vena cava ligation and subsequent operation together with the indications for further surgical measures and end results are shown in Table VI. The response of the extremities to therapy for thermal injury was well within the normal so that it may be assumed that in these patients, at least, cellular metabolism in the extremities was not altered by vena cava ligation. In the four patients requiring hysterectomy (total abdominal) the circulatory status through the lower abdominal wall and within the pelvis was thoroughly studied by us at the time of operation. In all four there seemed to be no increase in vascularity in the incised abdominal wall. The preperitoneal vessels were not engorged or congested and no deviation from normal status could be determined in the deep epigastric vessels except in one case. The broad ligaments in three of the patients were devoid of varicosities, whereas in one patient considerable dilatation of these vessels was noted. On removal of the uterus, in all cases, no more bleeding from the vaginal cuff or other areas was

TABLE VI. SUBSEQUENT SURGICAL PROCEDURES

PATIENT	V. C. LIGATED	SUBSEQUENT OPERATION	INDICATIONS	RESULTS
H. W.	12/31/48	Skin graft 2/12/49	3° burn left thigh Donor site right thigh	Healed 2/28/49 Asymptomatic
M. B.	10/30/44	Compression bandages 12/19/44	2° burn entire left leg	Healed, asymptomatic
G. A.	4/ 7/48	Dilatation and curettage 11/9/48	Bleeding retained secundines	Asymptomatic
M. S.	5/25/46	Dilatation and curettage 11/26/46	Polymenorrhea endometrial hyperplasia	Asymptomatic
J. D.	'42	Lobectomy '44	Lung abscess Residua of infarct	Died
E. P.	6/18/47	Lobectomy 6/30/47	Gangrene of lung Residua of infarct	Asymptomatic
E. W.	9/ 1/42	Laparotomy and plastic 3/3/46	Birth injuries Sterilization	Asymptomatic
D. P.	1/13/45	Cesarean section 11/4/48	Previous cesarean section	Mild ankle edema in evening
D. S.	8/29/48	Hysterectomy 8/29/48	Severe dyspareunia Chronic endocervicitis	Asymptomatic
P. H.	4/25/42	Hysterectomy 7/9/48	Pelvic pain, bilateral tuboovarian abscess	Asymptomatic
O. D.	5/ 2/42	Hysterectomy 7/30/42	Large fibroid	Asymptomatic
A. L.	4/30/42	Hysterectomy 6/15/47	Lower abdominal pain Chronic cervicitis Chronic bilateral salpingitis	Asymptomatic

encountered than at average routine abdominal hysterectomy. The visible retroperitoneal vessels did not seem to be engorged, congested, or varicosed. Palpation of the common iliac veins revealed them to be completely thrombosed and fibrotic in three of the four patients. In one, such was not the case and injection of Diodrast into the left common iliac vein and venography at the time of hysterectomy confirmed the experimental studies previously alluded to in that the major portion of the injected material was found in the lumbar and vertebral areas (Fig. 8). In the patient who had a vaginal plastic operation, suspension of the uterus, and tubal sterilization, and in the one requiring cesarean section, communications from their physicians informed us that there seemed to be no disturbed vascularity at the time of operation. Two patients required lobectomy for residual of the original infarctions which had necessitated ligation of the vena cava. One died at the time of lobectomy as a result of hemorrhage from the operative field; the other is well today. In two other patients in our series pulmonary abscesses developed as a result of the pre-caval ligation infarction but in both of these patients the abscesses healed spontaneously within two or three months, respectively. We are still undecided as to the efficiency of chemotherapy or antibiotics, or both, in the prevention of abscess in pulmonary infarction. In our first twenty-two cases chemotherapy or antibiotics, or both, were discontinued at the time of ligation in an attempt to prove that ligation alone was responsible for controlling the phlebitis. Pulmonary abscess developed in two of these twenty-two patients. In the remaining thirty-nine patients, chemotherapy and antibiotics were continued until the patient became afebrile in an attempt to forestall added pulmonary complications but pulmonary abscess developed in two of them.

Fig. 8.—Phlebogram of return circulation following ligation of inferior vena cava and ovarian veins taken at time of hysterectomy. Diodrast injected into left common iliac vein. Opaque hook-shaped object is catheter in bladder and urethra.

Condition of Vulva, Vagina, and Rectum

In none of the patients did varicosities or discoloration of the vulva, vaginal walls, or cervix occur. The only pathologic alterations noted in these structures at follow-up examination were those resulting from childbirth or infection. No

hemorrhoidal masses were observed. In patients with an uninfected cervix or vaginal wall, leucorrhea was not noted. No case of vaginal discharge could be attributed to "pelvic congestion." There was no change in any patient's psyche nor was there any alteration in the desire for, or reaction to, intercourse.

Menstrual Characteristics

Patients requiring operation to correct abnormal uterine bleeding and the pathologic condition encountered are listed in Table VI. One additional patient in whom the vena cava was ligated March 31, 1948, will require hysterectomy; vaginal examination disclosed a retrodisplaced, fixed uterus, and bilateral chronic salpingo-oophoritis; whether the abnormal bleeding is a result of the ligation or the pathologic condition described is a matter of conjecture. One patient has not menstruated since ligation of the vena cava, though none of her genital organs were removed at that time; extensive pyometritis associated with the suppurative process in the pelvic veins is believed to have destroyed the endometrium, resulting in amenorrhea. In all other patients the menstrual pattern is the same as prior to ligation of the vena cava.

Conclusions

1. Ligation of the inferior vena cava and ovarian vessels is indicated in patients with suppurative pelvic thrombophlebitis failing to respond to medical therapy, regardless of the severity of the illness.

2. Ligation of the vena cava in critically ill patients is associated with a low case mortality rate. The deaths in the present series occurred as a result of the pathologic condition for which operation was undertaken and not as a result of the operation *per se*.

3. The indications for operation in the patients requiring subsequent surgical procedures were not a result of ligation of the vena cava and ovarian vessels.

4. In our series there was adequate compensation for the circulation in the extremities following ligation. No patient was incapacitated.

5. Menstrual or sexual function was not altered by ligation in the majority of patients in our series.

6. Ligation of the vena cava and ovarian vessels (arteries and veins) appears to have little or no effect on ovarian function in women but further studies will have to be conducted to establish this observation definitely. The procedure does not preclude a normal pregnancy or postpartum course.

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Discussion

DR. RALPH A. REIS, Chicago, Ill.—Three years ago before this Society, Dr. Collins proved that patients would survive preoperative prophylactic ligations of the inferior vena cava and of both ovarian veins. Today he proved that such survival is usually followed by

good health and physical comfort. We believe that he failed to prove the need for such a procedure either as a prophylactic measure or as a therapeutic procedure for the cure of septic pelvic thrombophlebitis.

His original report quoted statistics from the literature in which postoperative pulmonary embolism occurred in 3 to 4 per cent following pelvic surgery. Of the deaths studied at Charity Hospital fifty, or 9 per cent, showed intravenous clotting and eight of these fifty had pulmonary embolism. Eleven patients with septic pelvic thrombophlebitis of obstetric origin were subjected to ligation of the inferior vena cava and of the ovarian veins. Two of these eleven patients died subsequently. In addition three patients with postoperative septic pelvic thrombophlebitis were treated in the same manner and all recovered. The present report concerns fifty-nine consecutive ligations with seven deaths. Because of these results, Dr. Collins recommends prophylactic ligations for large tumors with evidence of venous obstruction and pressure symptoms and further recommends similar ligations for septic pelvic thrombophlebitis since in his experience 85 per cent of such patients developed lung infarctions.

It is difficult to reconcile these figures and these recommendations with our own experience at Michael Reese Hospital. During the past ten years we have had 21,830 deliveries with seventeen deaths, or one death in each 1,284 deliveries. During this time pulmonary embolism was diagnosed only four times and, of these, one terminated fatally. This followed cesarean section, wound disruption, and sepsis. It would be most difficult to justify prophylactic vein ligations in any one of these 21,830 women.

Zimmerman, Miller, and Marshall have just reported the total Michael Reese Hospital experience with pulmonary embolism during the last seventeen years. Based on nearly 6,000 post-mortem examinations during this period in which 152,371 major surgical operations were performed, the incidence of fatal postoperative pulmonary embolism was 0.05 per cent, or one in every 2,000 major operations. Ten of these fatalities followed gynecological surgery and here again the incidence was approximately one in every 2,000 major gynecological operations. Five of these ten patients were suffering from malignancies of pelvic origin. It would likewise be most difficult to justify prophylactic vein ligations in this huge operative group.

The authors have stated that "Charity Hospital is a dumping ground" and that septic pelvic thrombophlebitis is relatively frequent and severe. We do not share in this experience. Michael Reese is a large general hospital with both private and service patients and our own experience with septic pelvic thrombophlebitis—both puerperal and postoperative is more limited than is our experience with pulmonary embolism.

It is difficult to accept the authors' dictum of venous ligations for this condition. Long experience of the European gynecologists led all but a small group in France to abandon venous ligations long before the last war. This was done because of the difficulties in diagnosis and because of the failure to improve their statistics. In Dr. Collins' paper, the mortality after ligations was given as 12 per cent. Our own experience gives a lower mortality without ligations, and one wonders how many patients were operated upon for the purpose of vein ligation who did not prove to have septic pelvic thrombophlebitis. It would seem, in this era of chemotherapy, antibiotics, and anticoagulants, that the addition of further surgical trauma to patients already critically ill from septic pelvic thrombophlebitis is unwarranted and may prove disastrous. One wonders why anticoagulants were used in "only a few cases."

In recent years we have been deluged with most enthusiastic reports of the merits of venous ligations for postoperative phlebothrombosis and thrombophlebitis; for example, one report of bilateral femoral vein ligations in 458 patients over 65 years of age followed by only one death from pulmonary embolism. In a comparable group of 458 without ligations, the thromboembolic syndrome occurred 58 times (1 in 8) and resulted in 26 fatal pulmonary emboli (1 in 17). Zimmerman and his group have estimated from their studies, that Michael Reese Hospital would have to have not 458 but 52,000 consecutive major operations to furnish the same number of deaths from pulmonary embolism. This means 1,140 times as many operations.

We venture the prediction that the ligation of major veins as prophylaxis or as therapy for puerperal and postoperative phlebothrombosis and thrombophlebitis will decrease in the coming years and that the enthusiasm for this procedure will steadily and rapidly wane.

DR. JOE V. MEIGS, Boston, Mass.—We see very few cases such as Dr. Collins has reported, but ligation of the vena cava is, and can be, done, but should not be, unless it is essential. Members of our hospital staff have recommended the ligation of veins as a prophylactic step to prevent embolism and in patients with vein involvement. Actually, we have done very few lately on our Gynecologic Service. Our patients now receive dicumarol in very moderate doses. However, if I had phlebothrombosis or an embolism which was not fatal I would choose to have my veins ligated. I would not care to take a chance on dicumarol or heparin if I knew I had a vein that was involved.

I think you have to ligate some veins and I agree that in some few cases we should ligate them prophylactically.

The more we watch and observe vein troubles the more we will be able to evaluate the procedure advocated by Dr. Collins. We will do fewer but we will not discard the procedure, I am sure.

DR. T. K. BROWN, St. Louis, Mo.—Ligation was done a few times in St. Louis in 1924 to 1928 without very satisfactory results. At that time the mortality throughout the country was about 50 per cent after such operations. This has been greatly improved where the operation is done more routinely, and I think one of the outstanding reasons for this improvement is that ligation has been done at an earlier time than it was in the past. Formerly it was a desperate procedure done as a last resort in most cases.

In 1924 Dr. Schwarz and Dr. Dieckmann showed the importance of anaerobic bacteria as the cause of thrombophlebitis in their work on puerperal infection. Shortly thereafter we were able to reduce the need for radical treatment in these cases if the uterus is treated early when it is the focus of infection, and if the site of infection is removed these subsequent complications have not occurred. Later the value of instillations of acriflavine and glycerine was shown, and since 1930 we have not had a death from thrombophlebitis on our service in St. Louis Maternity Hospital. Also since 1930 and with instillations of acriflavine and glycerine we have had no deaths from puerperal infection in some 37,000 deliveries. We have obtained similar results on our service at the St. Louis City Hospital No. 1, which is for white patients, and at Homer G. Phillips Hospital, where we see only Negro patients. These are both large services and we have not seen cases of severe thrombophlebitis or lung abscess in recent years. I would like to stress that the administration of sulfonamides and penicillin has played no role in the figures I have quoted.

DR. COLLINS (Closing).—We still see suppurative pelvic thrombophlebitis. I would like to emphasize that we saw many more than the forty-eight patients operated upon, but the latter were the ones that failed to respond to sulfonamides, penicillin, or streptomycin, and in a few cases dicumarol and heparin. In the pelvis where the disease process is not simply a clot but a suppurative process within a clot, that patient dies not of pulmonary embolism but of repeated small infarcts to the lung, liver, kidneys, and brain. If they do not respond to conservative treatment within five days ligation is necessary.

As regards phlebothrombosis or thrombophlebitis of the veins of the extremities, we do not use ligation or anticoagulants prophylactically to prevent embolism. We wait until clinical signs develop. There is no argument about anticoagulants as against ligation. The object is to prevent embolism and whether we use one or the other or both is immaterial. We believe if operation is to be of value in suppurative pelvic thrombophlebitis, five days is the limit of medical regimen.

Time does not permit a discussion of the diagnosis or pathology encountered.

INDUCED MENSTRUATION FOR METRORRHAGIA AND AMENORRHEA*

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THE treatments of metrorrhagia have been numerous and confusing. Probably the most common treatment is curettage of the uterus. This operation, removing the lining from the uterus, when done with care, may be followed in 50 to 60 per cent of the cases with excellent results. Particularly is this true if the irregularity in menstruation had been a minor one and of relatively short duration. The mechanism by which the ovary reverts to a normal cycle following curettage is not clear. The mechanical removal of the endometrium may interrupt some metabolic process of the hormones involving the retained endometrium or a nervous stimulation by a reflex method may cause the ovary to revert to normal or possibly the passage of time and improvement in general health following the temporary cessation of bleeding may have some indirect bearing on the return of the ovary to normal function.

Metrorrhagia can be readily controlled, according to Allbright,[1] by the administration of 5 mg. of progesterone daily for five or six days which will be followed three days later by a menstrual flow which leaves the uterus clean as though it had been curetted. This method of treatment he calls the medical curettage. It is also known somewhat in the literature as the Allbright curettage. In a single paper on this subject, in 1938, Allbright stated that this procedure prevented endometrial hyperplasia until such time as underlying disturbances in the ovarian cycle were corrected. He felt that the treatment did not correct, but merely took care of one of the complications of the disease. He thought progesterone helped in restoring the normal cycle. No cases were reported by Allbright. He stated that the method was first suggested by J. S. L. Brown. An abstract of a paper by Browne,[2] in 1938, in which he used 5 mg. of progesterone in four injections given every other day for the treatment of metropathia hemorrhagica, stated that a therapeutic curettage should first be performed. Otherwise there was a tendency for profuse bleeding following the first course of progesterone. He treated seven cases; two for twenty-eight and nineteen periods, the remainder for shorter intervals. Bleeding, normal in amount and duration, followed each course of injections in one to four days. These doses were inadequate to produce complete progestational change. In fact, little histological change was seen in the endometrium. Amenorrhea, associated with endometrial hyperplasia, was followed by normal periods of bleeding after progesterone thus given.

In three papers by Zondek and co-workers[3, 4, 5] (1938, 1940, 1942) dealing largely with the effects of progesterone on amenorrhea, further observations are important. He found that the administration of progesterone, 10 mg. daily for five days in the postmenstrual phase of the normal cycle, was followed in 60

*Presented, by invitation, at the Seventy-Second Annual Meeting of the American Gynecological Society, Hot Springs, Va., May 16 to 18, 1949.

hours by a period of apparently normal menstrual bleeding (intracyclic hemorrhage). If the progesterone was given while the patient had her own corpus luteum, bleeding either did not occur or occurred from a progestational endometrium. He felt there must necessarily be an interval between exogenous progesterone administration and endogenous hormone production. In secondary amenorrhea progesterone given 10 mg. daily for five days (in one case, 20 mg. for five days) was followed by an apparently normal menstrual flow. In primary amenorrhea no such bleeding occurred. He concluded that estrogen, though subnormal in amount, must be present for bleeding to occur after progesterone. Imperfectly proliferated endometrium responded to progesterone. Progesterone in doses of 50 to 150 mg. did not interrupt pregnancy. He stated that bleeding after 50 mg. of progesterone took place from a proliferative endometrium. The 50 mg. may be distributed over two days instead of five days. If given in one injection no result was obtained. Zondek felt that progesterone as a therapeutic agent was particularly valuable because it had no injurious effect on the anterior lobe of the pituitary gland and because any possible carcinogenic influence was eliminated. He thought that the progesterone dose (50 mg. minimum) may be reduced if the estrogen level in the body was increased.

In 1942 Allen and Heckel[6] reported the effect of progesterone in adolescent girls and young women with functional uterine bleeding. In twenty-four patients the administration of approximately 30 mg. of progesterone was followed by cessation of bleeding within ten days of the last injection. In one-third, normal cycles occurred for four months or more after therapy, whereas in another third there was a recurrence in less than four months. In the final third amenorrhea followed immediately or after two or three cycles. Treatment was given in courses intermittently. They felt that each course of injections acted similarly to a curettage of the uterus. They postulated that the progesterone might inhibit the estrogen to release the pituitary to more normal function, or that the sudden removal of inhibition from the temporary progesterone might be followed by greater gonadotropic function from the pituitary gland.

Jones and Te Linde[7] (1942) studied the subject of endometrial hyperplasia carefully. First they studied the effect of curettage alone in 111 cases. Approximately half of the group over 35 years was relieved by curettage alone. Of those under 35 years, 40 per cent were relieved by curettage alone. Twenty-eight were treated with progesterone after recurrence, and only two required hysterectomy. They found that progesterone would not control the immediate hemorrhage, and that its greatest use was for preventive purposes. Generally progesterone should be given cyclically for four months. They gave 5 mg. daily for ten days the first month, then for eight days, six days, and four days. Follow-up was by history and not by endometrial biopsy.

Rakoff[8] (1946) reported a series of 51 amenorrheic patients treated with progesterone, 20 mg. intramuscularly, daily for two and three days. Of 44 patients with secondary amenorrhea, 66 per cent responded to progesterone alone. Many of these had subsequent spontaneous bleedings and five became pregnant. The remaining 34 per cent had induced bleeding with progesterone after estrogen priming.

In the Endocrine Clinic of the University of Louisville in the last three years, an attempt was made to study this subject and to determine the value of progesterone in the treatment of functional uterine bleeding and amenorrhea. Various dosages and methods of giving progesterone were studied. The principle of this treatment consists first of the usual cessation of bleeding following continuous absorption of progesterone over three or four days. This is followed

by a period of withdrawal bleeding lasting three to seven days, after which complete cessation of bleeding occurs for a period of several weeks. It is important to understand that withdrawal bleeding follows the cessation of therapy, otherwise the patient and physician are under the impression that the treatment is of no value and has really made the condition worse in many instances. Once the prolonged bleeding has been stopped, repeated administrations of progesterone are given every twenty-eight days, each in turn being followed by withdrawal bleeding which one may predict with reasonable accuracy according to the dose and type of product used.

Puberty Metrorrhagia

There were eight cases with puberty metrorrhagia. Two were 12 years of age, three were 15, one was 16, one was 17 and one was 19 years old. The older patients had had continuous or almost continuous bleeding since menarche. Three were curetted originally. In four, the first withdrawal bleeding with treatment was not excessive, while in one the first withdrawal bleeding was excessive, requiring transfusions.

These eight patients were treated with courses of progesterone for a total of fifty-three cycles. The largest number of courses (twenty-three) was with progesterone 10 mg. in oil intramuscularly daily for five days. Continuous withdrawal bleeding occurred for five to seven days, or if the patient was not bleeding at the time, simple withdrawal bleeding followed an average of three days later. Similar withdrawal bleeding followed progesterone in doses of 12.5 mg. or 25 mg. in oil daily for five days, also after 25 mg. in oil for three days. Progesterone, 20 mg. aqueous suspension for one dose on three occasions, or three daily injections, induced withdrawal bleeding. Thirteen bleeding episodes followed progesterone, 50 mg. in beeswax-peanut oil, although in three the onset was delayed for fourteen and fifteen days. A single injection of 125 mg. in oil was followed by withdrawal bleeding in two of three cases. In one, apparently the absorption and excretion were too rapid. In one, 125 mg. in oil for two days gave the usual normal withdrawal flow. Four courses of sublingual progesterone were tried, failing with 25, 30, and 50 mg. daily for five days, but giving the usual withdrawal bleeding after 100 mg. for five days.

In three patients biopsies taken before treatment showed endometrial hyperplasia. Sixteen series of biopsies were taken after administration of progesterone. In two, late interval (or early progestational) endometrium was found four days after 125 mg. in oil. One of these biopsied on the sixth day, while bleeding, showed fragmented menstrual-type endometrium, representing a very rapid change to the disintegrated endometrium as found during normal menstruation. The other case had no withdrawal bleeding, possibly because of too rapid absorption and excretion of the single dose in oil; the biopsy on the seventh day showed interval nonsecretory endometrium, reverting from early secretory to nonsecretory intact endometrium in three days. After progesterone, 125 mg. in oil for two days, fragmented menstrual endometrium with some Swiss cheese glands with basal globules were found. After progesterone, aqueous suspension 20 mg. for one day, menstrual fragmenting endometrium was found in two and questionable secretion in a third. When the same dose was given for three days a full premenstrual endometrium occurred seven days later. After 10 mg. in oil intramuscularly daily for five days, premenstrual endometrium was found in one, nonsecretory in one, and insufficient tissue after bleeding in a third. After 12.5 mg. daily for five days, a late interval endometrium (early progestational) mixed with Swiss cheese hyperplasia was followed by fragmented menstruating endometrium during bleeding. Fifty mg. of progesterone in beeswax-

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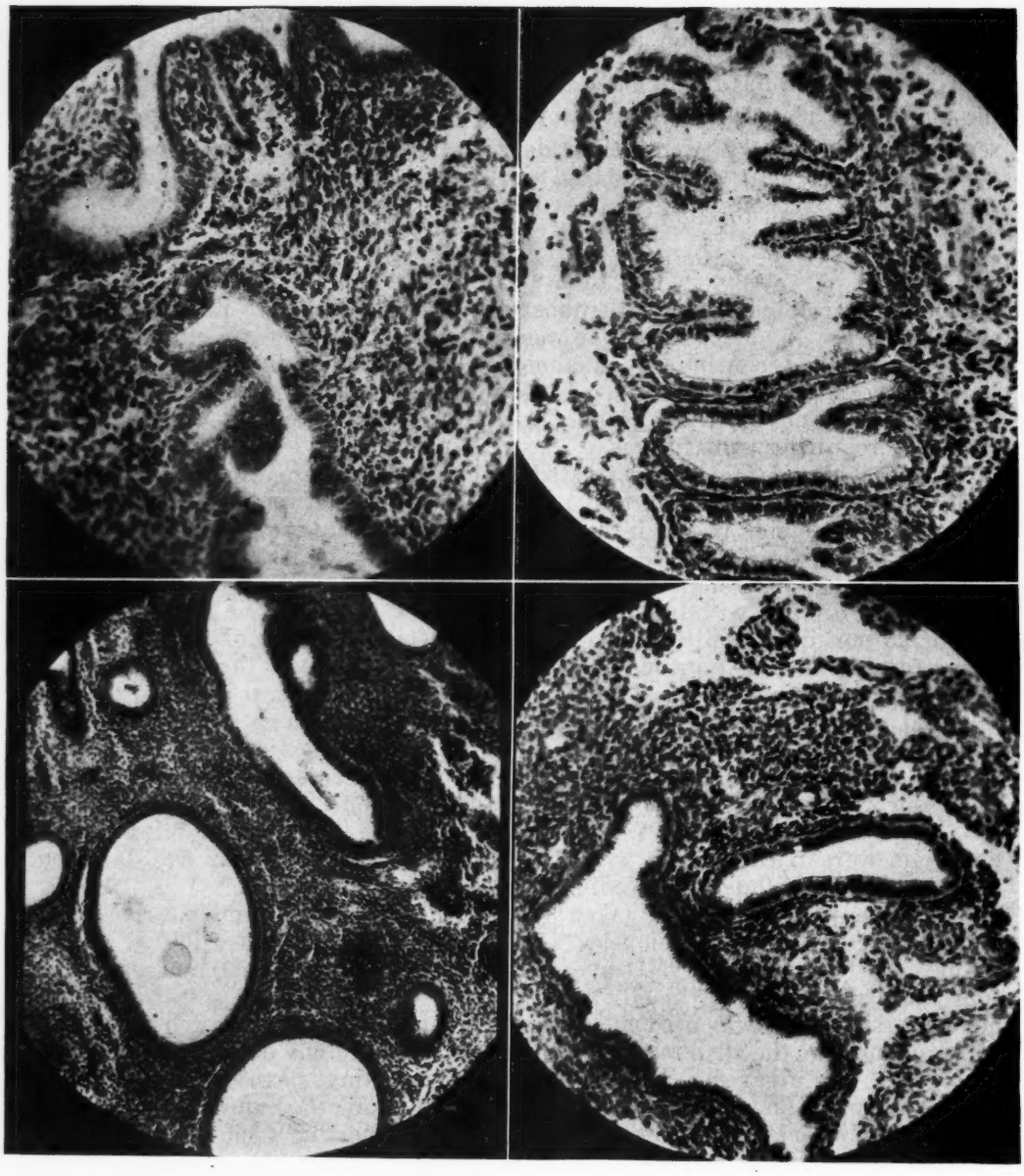

3. 4.

Fig. 1.—Patient H. Y., aged 17 years, Metrorrhagia. Before treatment No. 46-1585. Nonsecretory endometrium with hyperplastic glands; continuous bleeding.

Fig. 2.—Patient H. Y., eight days after biopsy (Fig. 1) and three days after progesterone, 10 mg. intramuscularly daily for five days. No. 46-1621. Premenstrual endometrium. Bleeding ceased after third injection and withdrawal bleeding began after this biopsy.

Fig. 3.—Patient H. Y., no recent treatment. No. 47-1347. Endometrial hyperplasia.

Fig. 4.—Patient H. Y., progesterone 125 mg. intramuscularly daily for two days. Second day later, No. 47-1410. Endometrial hyperplasia with some basal globules indicating partial early secretion.

peanut oil was followed by nonsecretory endometrium in one, and insufficient tissue during bleeding in the second. After 100 mg. sublingually for five days, insufficient tissue could be obtained during withdrawal bleeding. After 30 and 25 mg. combined with Urestrin, sublingually for five days, the endometrium remained nonsecretory and no bleeding occurred.

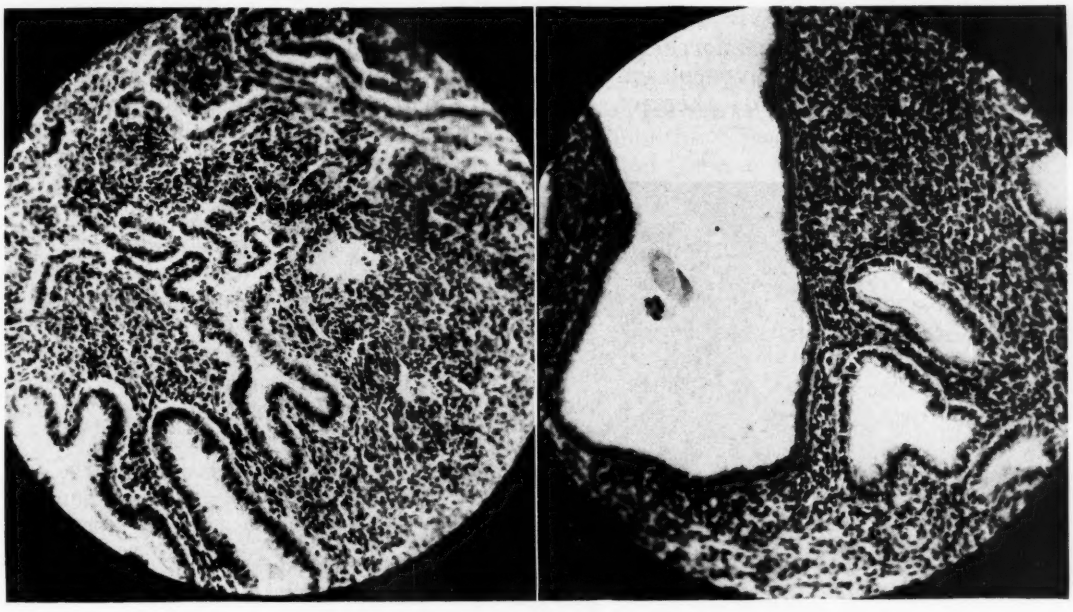

Fig. 5. Fig. 6.

Fig. 5.—Patient H. Y., fourth day after progesterone. No. 47-1412. Menstruating endometrium with fragmentation and hyperplasia background.

Fig. 6.—Patient H. Y., progesterone 12.5 mg. intramuscularly for five days. Biopsy day of last injection, No. 48-85. Late interval (early secretory) with some Swiss cheese nonsecretory glands.

Secretory endometrium was found after progesterone on eight occasions, and menstruating fragmenting endometrium in five biopsies. Insufficient tissue was obtained three times during bleeding, possibly meaning most of the endometrium had been shed. Nonsecretory tissue was found twice after intramuscular progesterone and after sublingual progesterone when the dose was 50 mg. or less daily for five days. In two above instances secretory changes occurred on a background of Swiss cheese type hyperplasia.

Follicle-stimulating hormone studies were made in three cases. In one patient the titer was high (+53 mouse units per liter), normal (+6.6) and too low (–6.6) in the three samples tested. In the second it was low twice (–6.6), normal twice (+6.6, –53; +6.6). In the third it was low (–6.6). With endometrial hyperplasia and supposed hyperestrinism, one might have expected consistently high values.

Pregnandiol studies showed rapid excretion after 125 mg. intramuscularly, after one day 16 mg., after two days 5.6 mg., and after eight days 1.1 mg. When progesterone, 50 mg., was given in beeswax-peanut oil, the level rose slowly, 2.2 mg., 3 mg., 8 mg., 13 mg., 25 mg., 8 mg., 16 mg., and 0.4 mg. being found on successive days. Progesterone, 100 mg. sublingually for five days, resulted in an excretion of 16.5 mg. after one day of therapy, 10.3 mg. after two days, 16.5 mg. after three days. Two days after cessation there were 4.5 mg., three

days 4.5 mg., and six days 2.8 mg. A marked rise in pregnandiol excretion occurred during sublingual therapy but this rapidly subsided after cessation of therapy. Apparently one injection in oil gives a rapid rise and fall in two days, whereas the beeswax-peanut oil preparation gives sustained excretion levels.

In these eight cases the bleeding was controlled readily with progesterone. Three to four series of treatments in four patients were followed by practical cure (two received thyroid). In a fifth, recurrence followed after six months. The sixth developed amenorrhea. In the last two (aged 17 and 19 years) recurrence of endometrial hyperplasia and metrorrhagia has followed extensive progesterone (and thyroid) therapy. They have had a total of nine and eleven treated cycles.

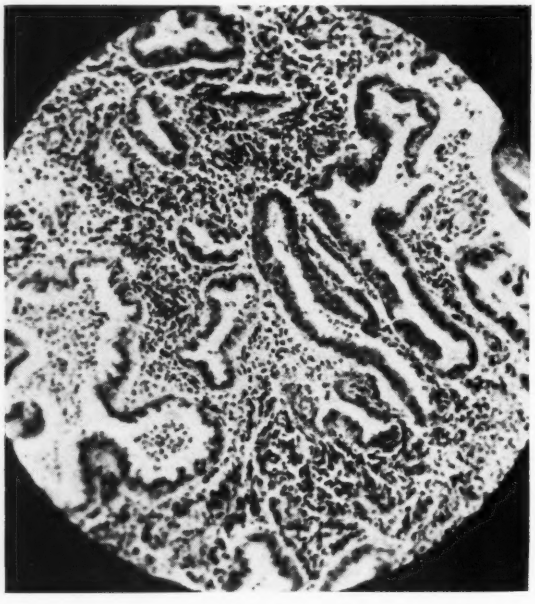

Fig. 7.—Patient H. Y., third day later (after Fig. 6). No. 48-104. Menstruating endometrium with fragmentation and secretion.

Progesterone therapy has given excellent control of bleeding in puberty metrorrhagia. In two of the older patients, permanent cure has by no means been effected. Further controlled bleeding seems indicated in these in order to avert hysterectomy. Possibly spontaneous reversion to ovulatory cycles will occur.

Metrorrhagia After Puberty

There were thirty cases with metrorrhagia. This group includes those with prolonged bleeding which occurred after puberty as distinguished from the other group of puberty bleeders which began practically with the first menstruation. In this group of thirty cases, fifteen were in the twenties, eleven were in the thirties, and only two were over forty. Sixteen patients were treated for only one cycle. Of these, eight had good results for six months or longer, one having recurrent metrorrhagia after six months. Half of these patients were also given thyroid therapy. Six of this group treated with one series of progesterone had recurrence of metrorrhagia within one to three months. Two were not followed for a sufficient period of time. It is to be noted that six of this group had minor metrorrhagia.

Two patients were treated for two months, each followed by withdrawal bleeding and controlled bleeding at the time, but they have not been followed sufficiently.

Twelve patients were treated for three months or longer. Actually three were treated for three months, four for four months, two for five months, one for six cycles, one for seven cycles and one for fourteen cycles. These treatments were not always consecutive but usually given for one to four months at the time. Of the three patients treated for three months, controlled bleeding without intermenstrual bleeding occurred but they have not been followed sufficiently to determine cure. Of the four patients treated for four cycles, three were cured and the fourth had a recurrence after five months. Two of these four were treated with thyroid. Two patients were treated for five cycles; one was cured over a prolonged period of time subsequently, and one has had an insufficient follow-up. One patient was treated for six cycles and later had a recurrence after five normal cycles. Thyroid was given to this patient. One patient was treated for seven cycles, and has been considered cured after prolonged follow-up. She is also taking thyroid. The last patient was treated for fourteen cycles intermittently. During the treatment, short series of normal cycles occurred followed by amenorrhea and recurrent metrorrhagia three separate times. No thyroid was given this patient. While this extensively studied case certainly has not been cured, bleeding has been controlled over a period of two years to her great satisfaction and with little abnormality.

In this group of thirty cases there were eighty-four treated cycles. Thirty-four were treated with progesterone, 10 mg. in oil intramuscularly daily for five days. There was no failure of withdrawal bleeding, the onset of which varied from one to eight days following the last injection, and in half the withdrawal bleeding began within two to three days after the last injection. There were six continuous withdrawals in which the hormone was given during the prolonged metrorrhagia. The bleeding stopped from one to five days after the last injection.

There were fourteen cycles treated with 50 mg. of progesterone in beeswax and peanut oil, given as one injection. There were seven normal withdrawal bleedings occurring in from three to eleven days. Two were three days later, two six days later, one eight days later, one ten days later, and one eleven days later. There were seven cycles of treatment given while bleeding was in progress, and the bleeding ceased from two to thirteen days later. It is to be noted that the withdrawal effects are more delayed after the beeswax, peanut oil preparation. In fact it is more prolonged than desirable.

There were nineteen courses of treatment given in miscellaneous manners, including 125 mg. in oil in one injection, 100 mg., 50 mg., in one injection, 25 mg. daily for five days, aqueous progesterone 20 mg. in one injection, and aqueous progesterone 60 mg. in one injection. Sixteen of these were followed by withdrawal bleeding in from one to nine days, the most prolonged being that following one injection of 60 mg. in aqueous suspension. There were three continuous withdrawal bleedings when the injections were given in the course of metrorrhagia. Satisfactory withdrawal effects followed all of these injections although in some the effects were delayed.

There were seventeen courses of treatment with sublingual progesterone. There were four failures following 30 and 50 mg. sublingually for five days. Withdrawal bleeding did occur in the remaining five cases with 30 mg. and 50 mg. sublingually for five days. Better results followed 100 mg. daily for five days, but in four instances the withdrawal bleeding was delayed for nine, twelve, and thirteen days, and three times was quite scant.

Endometrial studies before treatment showed interval nonsecretory endometrium or endometrial hyperplasia in nineteen patients. Biopsies were made

following eighteen courses of treatment. In five, normal-appearing late interval (early progestational) or premenstrual endometrium was obtained. In five other cases, biopsies taken during bleeding showed typical fragmented menstruating endometrium as is seen in the normal menstrual phase. Four other cycles that were studied were labeled as follows: probable early secretion, hyperplasia background with some tendency to saw-tooth glands, subnuclear vacuoles in otherwise nonsecretory appearing endometrium, and slight secretion with interspersed hyperplastic glands. Biopsies made during bleeding after three other courses of treatment showed insufficient tissue, possibly indicating that the endometrium had been largely shed from the uterus. There was only one proved nonsecretory effect in the eighteen biopsies and this followed 100 mg. of progesterone sublingually for five days. While the effects of progesterone on the endometrium are not consistent in that all cases show the same degree of progestational change, yet the vast majority do show some definite secretory changes in the endometrium, varying from a slight secretion with the hyperplasia background to the well-developed premenstrual endometrium, at times with decidua-like stroma, to the fragmented menstrual type of endometrium.

Hormone studies were made in some of the patients in this group. Seven patients had follicle-stimulating hormone studies which were all inconclusive. In one, tests were normal six times and high once. In the second, six tests were all normal. In the third, three tests showed once normal and twice high. In the fourth, one test showed too much (more than 85 mouse units per twenty-four hours). The fifth, with three tests, was normal. In the sixth, four tests showed one too high. In the seventh, three tests were above normal and one was normal.

Pregnandiol studies of the urines were made in a number of instances following progesterone administration. After progesterone, 10 mg. intramuscularly daily for five days, the level rose to 9.8 mg. in three days and dropped to 4.1, four days after the last injection. When progesterone, 50 mg. in beeswax and peanut oil, was given as one injection the level rose more slowly in two instances, one up to 20 mg. four days later and remaining at 8.9 mg. on the eighth day. Two other series showed very little rise (to 3.9 mg.). Progesterone, aqueous suspension 60 mg. in one injection, showed a delayed rise to 8 mg. on the fifth day with 4 mg. on the eighth day. Another series showed a rise to 9 mg. on the third day and 3.4 mg. on the fourth day. Progesterone, 20 mg. aqueous given daily for three days intramuscularly, showed a rise to only 3.3 mg. on the third day. Progesterone, 100 mg. in benzyl benzoate given in one injection, showed a rise the next day to 37.8 mg. Four days after the injection it was 7.2 mg. This suggested a remarkable increase in progesterone absorption. Eight courses of sublingual progesterone showed little or no effect after 20, 30, and 50 mg. daily sublingually but after 100 mg. daily the level rose after four days of treatment to 16.5 mg. and 47.6 mg. in two cases and on the eighth day of treatment to 13.8 mg. in the third case. While these tests are insufficient to be conclusive, they suggest that the administration of progesterone, 10 mg. in oil daily for five days, will maintain a rise over three or more days. In the beeswax and peanut oil a single injection may result in sustained rise even after eight days, which may explain the bleeding delayed for fifteen days in some instances. The aqueous progesterone was followed by a delayed rise for four days which probably explains why withdrawal bleeding usually follows this single type of injection. The sublingual administration of 100 mg. daily does show a remarkably high excretion of pregnandiol and may indicate that satisfactory results should follow this treatment, but it has not been studied sufficiently as yet.

One may conclude that progesterone therapy is exceedingly satisfactory in stopping bleeding in from three to ten days following the last administration of progesterone, and that withdrawal bleeding will occur, when no bleeding is

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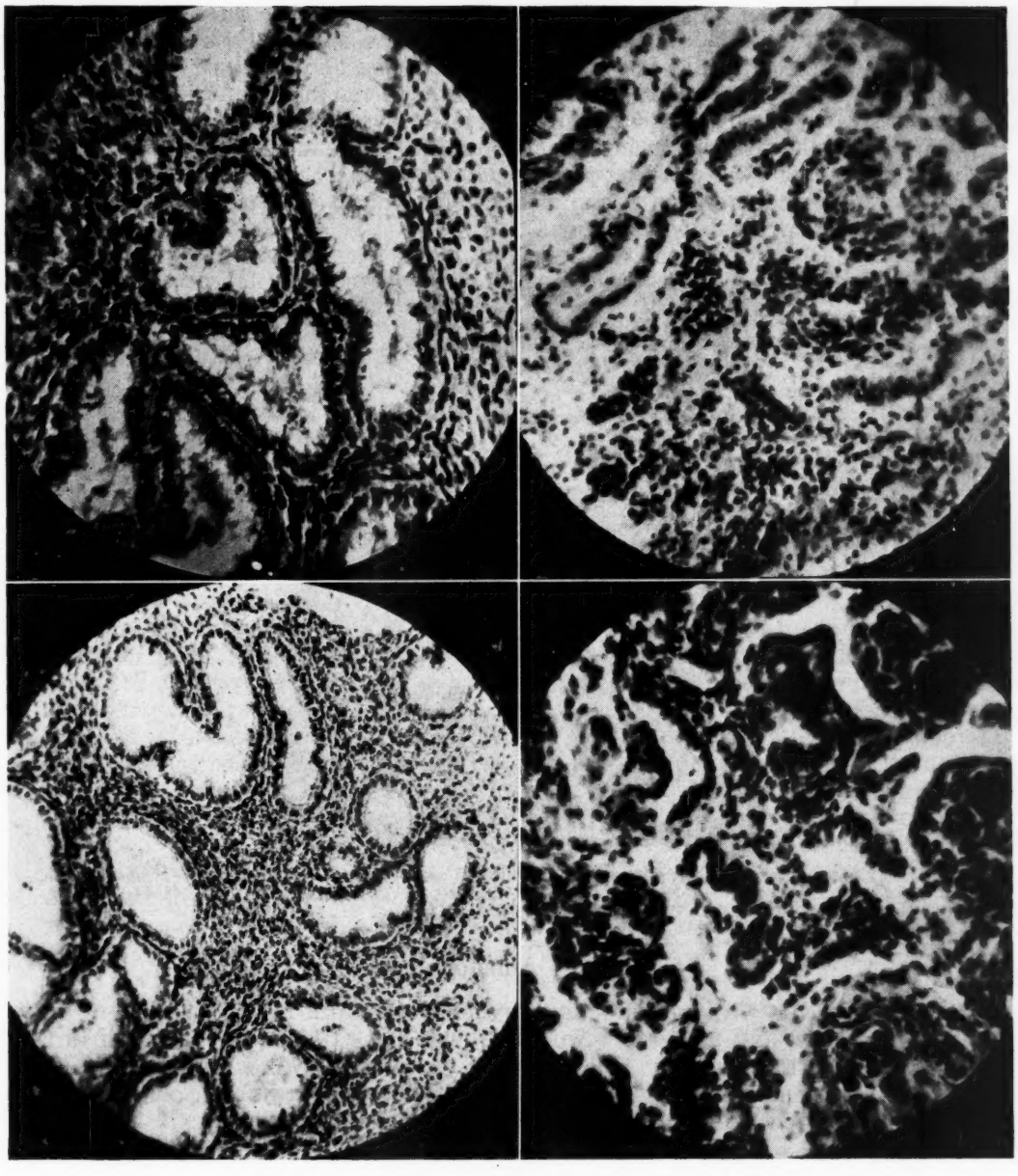

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Fig. 8.—M. F. C., aged 15 years, metrorrhagia, endometrial hyperplasia. Progesterone 125 mg. intramuscularly one day. Fourth day later, No. 47-1533. Late interval (early secretory) endometrium.

Fig. 9.—M. F. C., seventh day after progesterone (after Fig. 8). No. 47-1551, menstruating endometrium. Bleeding began.

Fig. 10.—M. F. C., progesterone, 20 mg. aqueous suspension intramuscularly every other day for three injections. Biopsy three days after last injection, No. 48-193, premenstrual endometrium. Bled two days later.

Fig. 11.—M. F. C., progesterone, 20 mg. aqueous suspension intramuscularly for one injection. Biopsy seven days later, No. 48-553, menstruating endometrium. Period began.

in progress, on the average of three days later. It tends to be delayed after aqueous suspension, beeswax-peanut oil, and sublingual preparations. Of these thirty cases, thirteen have been considered cured. Seven of these patients had thyroid in addition. While cure may not always be expected with this method it does offer excellent control of bleeding, until nature may produce the reversion to normal. Secretory changes were produced in the endometrium in practically all cases treated in this series although there was variation in the response. It appears that the fragmentation that occurs in the endometrium during the normal menstrual cycle may be produced by progesterone. The changes from early secretory endometrium to the menstrual fragmentation may be very rapid in the course of two or three days' time.

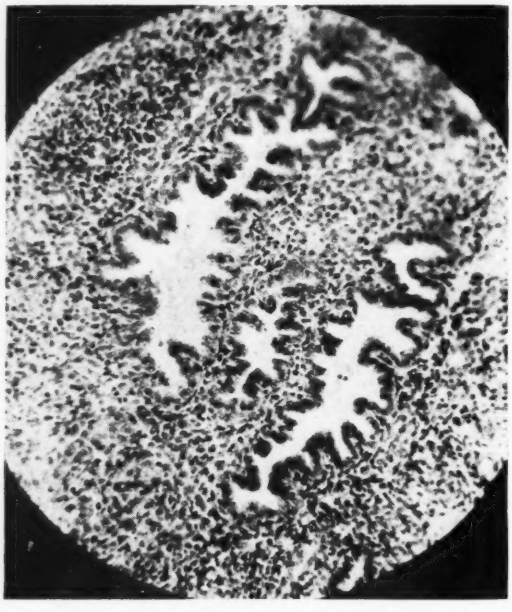

Fig. 12.—M. B., aged 26 years, metrorrhagia, endometrial hyperplasia. Progesterone, 100 mg. in benzyl benzoate for one injection. Biopsy seven days later, No. 48-1100. Premenstrual endometrium. Bled two days later.

Primary Amenorrhea

Seven patients with primary amenorrhea were studied. The ages were 17, 18, 19, 20, 23, 27, and 28 years. None had ever menstruated. Six showed thin vaginas and castrate smears. One (aged 17 years) had a thick vaginal mucosa with full estrogenic smear. Twenty-three courses of progesterone with added estrogen were given, followed by withdrawal bleeding sixteen times.

Six courses of progesterone 10 mg. with Urestrin, 10,000 I.U. (Cyclogesterin, Upjohn) daily for five days were followed by withdrawal bleeding five times and no bleeding once. Five courses with progesterone 12.5 mg. with estradiol benzoate 2.5 mg. (Prometron, Schering) daily for two days were followed by withdrawal bleeding three times and none twice. Aqueous suspension of progesterone 25 mg. with Urestrin 25,000 I.U. (Upjohn) for one dose produced bleeding once, for two doses produced no bleeding twice, for five doses produced bleeding once. Aqueous progesterone, 25 mg. for five doses, in a patient taking estrone sulfate continuously was followed by withdrawal bleeding once. In three patients primed with estrone sulfate (Premarin) withdrawal bleeding followed three times after progesterone, 50 mg. in beeswax-peanut oil.

Progesterone, 50 mg. in beeswax-peanut oil alone, and sublingual progesterone alone were followed by no bleeding. Sublingual progesterone, 100 mg. daily for five days, in a patient receiving Menagen (Parke, Davis & Co.) continuously had withdrawal bleeding twice. It seemed evident that these patients with primary amenorrhea and a thin vaginal mucosa must receive estrogen to prime the endometrium. Even then withdrawal bleeding was not constant.

Follicle-stimulating hormone assays were normal in two, and too high in two (more than 53 mouse units in twenty-four hours), suggesting that two were pituitary failures and two were ovarian deficiencies.

All seven patients received thyroid. Six with atrophic vaginas were not benefited except psychologically with the temporary bleeding. One (aged 17 years) with a thick vaginal membrane originally, continued to menstruate normally with thyroid, 2 grains daily. This patient probably should not be considered as having primary amenorrhea but delayed menarche.

Secondary Amenorrhea

Thirty-one patients with secondary amenorrhea were treated with progesterone. The ages varied from 17 to 42 years. The majority were between 20 and 30 years. One hundred eighteen courses of progesterone were given, followed by withdrawal bleeding ninety-five times.

Various preparations and doses of progesterone were given. Ten mg. in oil intramuscularly daily for five days were followed by withdrawal bleeding after sixteen of eighteen courses, an average of three days after the last injection. The same dose with Urestrin added (Cyclogesterin, Upjohn) was followed by bleeding six out of seven courses, but was delayed three times for ten, eleven, and fourteen days. Progesterone, 12.5 mg. for two injections, with added estradiol benzoate 2.5 mg. (Prometron, Schering) produced bleeding after nineteen out of twenty-one courses, an average of three days later. Progesterone, 20 mg. aqueous suspension with Urestrin, 20,000 I.U., as one injection, was followed by bleeding sixteen out of seventeen times, varying from two to seventeen days later, averaging eight days. Progesterone, 25 mg. aqueous suspension with Urestrin 25,000 I.U. for two injections, was followed by bleeding thirteen out of fifteen times, from two to seventeen days later. Progesterone, 50 mg. in beeswax-peanut oil, was followed by withdrawal bleeding twelve of fifteen times, occurring three to ten days later, averaging five days. Progesterone, 125 mg. in oil as one injection (in 5 c.c.), was followed by normal bleeding once, scant bleeding once, and no bleeding twice. Progesterone, 50 mg. in benzyl benzoate daily for three days, was followed by bleeding two to four days later. Six failures of withdrawal bleeding followed sublingual progesterone given 25 to 50 mg. daily for five days. One hundred mg. sublingually were followed by withdrawal bleeding three times, one time scant.

Premenstrual or late interval secretory endometrium was found three times and nonsecretory endometrium once after progesterone, 10 mg. intramuscularly daily for five days. Progesterone, 50 mg. in beeswax-peanut oil, was followed by late interval secretory endometrium one time and insufficient tissue twice during bleeding, possibly meaning that the endometrium had been shed. After progesterone, 20 mg. aqueous suspension for two days, endometrial hyperplasia persisted in one case.

Follicle-stimulating hormone assays were normal in one case, low in one case (less than 6.6 mouse units) and high repeatedly in three cases (more than 53 mouse units).

Eight of the thirty-one patients showed slight atrophy of the vagina before treatment, but only one of these had no withdrawal bleeding after progesterone. The others were thought to have a normally thick vagina. Seventeen of the

thirty-one patients were considered unimproved after treatment. Eight of these had received thyroid. Three of the seventeen subsequently developed progressive atrophy of the vagina and were thought entering an early menopause. Seven have been observed an insufficient time. Only eight patients have been considered improved or cured. One has become pregnant and five have been maintained on thyroid therapy. It is evident that progesterone alone will produce withdrawal bleeding, if absorbed over a period of three, four, or five days. Subsequently normal cyclic menstruation may follow in a minor percentage of cases.

Comment

The above summaries illustrate the use of progesterone in the treatment of metrorrhagia and amenorrhea. It is evident that in the majority of these patients if an increased level of progesterone is maintained over a period of three or four days or more, a drop in the level will be followed by withdrawal bleeding, provided there is a moderately subnormal or higher level of estrogenic hormone present. If estrogens are absent, as in the true primary amenorrhea, no bleeding will follow. Also, the antibleeding effect of increasing levels of progesterone is useful in controlling prolonged bleeding in progress.

In this group of patients progesterone has been given in various forms in 278 courses. Continuous bleeding at the time the progesterone was given was followed twenty-one times by either cessation of bleeding on the third day and subsequent withdrawal bleeding three to five days later, or by continuous withdrawal bleeding for two to thirteen days. Delayed withdrawal bleeding at times followed progesterone, 50 mg. in beeswax-peanut oil or 60 mg. in aqueous suspensions. Added estrogens caused delayed bleeding in some cases. Evidently the beeswax and aqueous-suspension preparations may be too slowly absorbed and excreted for prompt decisive withdrawal bleeding. In only three instances was the first withdrawal bleeding unduly profuse, all aided by testosterone at the time, and one child received transfusions.

Expected withdrawal bleeding failed to appear after thirty-four series of treatments. Twenty-seven of the failures were in primary and secondary amenorrhea where a total of 141 series were given. Only seven failures were among the metrorrhagia groups. One received 125 mg. as one injection, and the absorption and excretion were undoubtedly too rapid. Six failures were after sublingual progesterone in doses of 50 mg. or less daily for five days.

Progesterone therapy is particularly applicable for control of metrorrhagia, especially in puberty bleeding. The most consistent results followed 10 mg. intramuscularly for five days, repeated at twenty-eight day intervals for three or four months. Various other forms listed above will produce satisfactory hemostasis and withdrawal bleeding, but the time intervals are not nearly as consistent. A single injection in oil is not satisfactory because of too rapid absorption and excretion. From beeswax-peanut oil, absorption is slow, results are satisfactory but the onset of withdrawal bleeding may be delayed an average of eight days, and occasionally as long as seventeen days. Following progesterone in aqueous suspension the results are frequently not as predictable. A product that will produce just the proper increase of progesterone for more than three days and less than six days is desirable for single injection medication. Aqueous progesterone is the nearest solution, although this particular product at times produces marked local pain. Certainly bleeding may be completely controlled and such control may be continued as long as necessary. It is realized that puberty metrorrhagia may last a few months or few years, but usually is spontaneously cured. This apparently innocuous therapy may be maintained as long as necessary. During this treatment anemia may be corrected, weight

be regulated, and thyroid be given as indicated. It is possible that subsequent gonadotrophic therapy may be important under this control. There is no clear evidence from these clinical findings that progesterone stimulates pituitary function or indirectly produces ovulation.

In amenorrhea, therapy has been less satisfactory. In true primary amenorrhea there is no ovarian function and the patients are probably castrates at the start. Withdrawal bleeding occurred only if added estrogens were given, at least in small amounts. None of these patients with atrophic vaginas was cured. On the other hand, estrogens developed secondary sex characteristics and progesterone withdrawal bleeding was of psychological value. In secondary amenorrhea there is estrogen present, unless the patient has progressed to a premature menopause. Usually bleeding follows progesterone, in some cases estrogens must be added, but the results still are not consistent. After varied courses of treatments only eight of thirty cases with secondary amenorrhea were considered cured, and certainly thyroid therapy was an important factor in five.

Endometrial biopsies after progesterone showed secretory effects in twenty-seven series, insufficient tissue seven times during bleeding which may have indicated that most of the tissue had been shed, and no change in the nonsecretory endometrium seven times. Premenstrual or late interval secretory endometrium appeared quite normal thirteen times. Menstruating fragmenting endometrium was found eight times during bleeding on the first biopsy after treatment. Three showed quite early secretory changes as evidenced by subnuclear vacuoles in only part of the glands. Three showed a mixed late interval endometrium superimposed on a hyperplasia Swiss cheese background. Complete absence of secretion occurred in seven, after progesterone, 10 mg. intramuscularly for five days (two), progesterone 50 mg. in beeswax-peanut oil (one), progesterone 40 mg. in aqueous suspension (one), and progesterone sublingual 30, 50, and 100 mg. for five days (three). In contrast to the observations of others, secretory changes were common after progesterone therapy.

Menstruating-type endometrium with its marked fragmentation and necrosis, acute inflammatory cells, and disruption of glands lined by a single layer of cuboidal epithelium seemed a characteristic of progesterone bleeding. This is in contrast to the bleeding from relatively intact nonsecretory endometrium as seen in biopsies or the excised uterus. In one case this fragmenting endometrium was found on the sixth day after progesterone, 125 mg. intramuscularly. On the fourth day (two days previously) biopsy showed late interval secretory endometrium, such as is found about the twentieth day of the cycle. In another case nonsecretory endometrium preceded this fragmenting endometrium by three days. It seems likely that the diffuse fragmentation and necrosis of normal menstruation are caused by progesterone.

Hormone studies in this laboratory are not complete. References are made above to follicle-stimulating hormone determinations. The results were so variable that no conclusion is drawn. Pregnandiol studies have given some suggestions. The Guterman test for free pregnandiol was used throughout.

After 125 mg. in oil as one injection, the pregnandiol was 16, 5, 6, and 1.3 mg. on successive days. After 10 mg. in oil intramuscularly daily for five days, findings were negative qualitatively throughout or negative, negative, positive, negative, negative on successive days. After 50 mg. in beeswax-peanut oil, the pregnandiol rose to 3.9 and 4.5 mg. on the fourth day, but in one was 20 mg. on the fourth day and 9 mg. on the eighth. After aqueous progesterone 20 mg., negative results or very slight increases to 3 mg. were found. After 60 mg. aqueous suspension, there were rises to 8 and 9 mg. on the third and fifth days. After sublingual progesterone the pregnandiol recoveries were greater. After

25 and 30 mg. daily for five days, the findings were negative throughout or showed an occasional positive qualitative test. Two showed increases to 5 and 6 mg. on the third day. After 100 mg. daily sublingually, the pregnandiol rose on the third day of therapy to 10, 18, 6.3, 11, and 22 mg. in different cases. One increased to 36 mg. on the fourth day, 26 mg. on the seventh. Another increased to 34 mg. and 33 mg. on the fourth and fifth days. One patient who swallowed 100 mg. daily had a rise to 47 mg. on the fifth day. The injectable progesterone has seemed to give very slight rises in pregnandiol excretion, although apparently greater after beeswax-peanut oil and aqueous suspension preparations. The increases after the much larger doses given sublingually were remarkable and merit further study.

Summary

1. Progesterone has been given in various forms as 278 courses of treatment in seventy-six patients.

2. Antibleeding effects during metrorrhagia and withdrawal bleeding effects have been utilized in controlling metrorrhagia and amenorrhea.

3. Of eight patients with puberty metrorrhagia, four were apparently cured, one had recurrence after six months, and one developed amenorrhea. Two were not cured, being controlled only as long as progesterone was given.

4. Of thirty cases with metrorrhagia after puberty, thirteen were considered cured (seven received thyroid).

5. Of seven patients with primary amenorrhea, one was cured. This patient had an estrogenic vaginal mucosa before treatment and probably had only delayed menarche.

6. Of thirty-one patients with secondary amenorrhea, eight have been considered improved or cured (five received thyroid).

7. Progesterone produces a menstruating type of endometrium with fragmentation and necrosis, which apparently clears the uterus of the superficial layers of endometrium.

8. This useful procedure controls bleeding accurately, but cure apparently depends on spontaneous reversion to normal, aided in some cases by correction of abnormal weight changes, and the administration of thyroid as indicated.

Note: The Endocrine Laboratory of the Department of Obstetrics and Gynecology of the University of Louisville Medical School has been aided for the past three years by generous grants from The Upjohn Company and Ayerst, McKenna and Harrison, Ltd. Progesterone has been supplied by The Upjohn Company, Ayerst, McKenna and Harrison, Ltd., E. R. Squibb & Sons, and the Schering Corporation.

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Discussion

DR. CARL P. HUBER, Indianapolis, Ind.—The management of functional uterine bleeding and amenorrhea has been the source of so much confusion in past years that every contribution which gives us additional controlled information is welcome. Quite obviously the method of therapy presented today is not the final answer. There were a considerable number of failures in all age groups. Definite conclusions cannot be drawn concerning dosage, method of administration, or predictability of results. This is equally true of other methods of treatment which have been suggested.

At the present time several plans of management for menometrorrhagia are in vogue and each has ardent advocates. Estrogens are used alone or in combination with progesterone. Androgens are used alone or also in combination with progesterone. In the present presentation, progesterone is used alone. In the light of our present knowledge of ovarian physiology a reasonable explanation can be given for each. Bleeding will temporarily cease following treatment according to any one of these plans but recurrences are frequent and upon occasion more radical methods become necessary. Nearly all support the additional use of thyroid where hypometabolism is present.

The author presents evidence to support the idea that the administration of progesterone in sufficient effective doses results in a more nearly normal menstrual slough of the endometrium than that which follows other types of therapy. This same pattern is seen when progesterone is used in combination with either estrogenic or adrogenic substances. He is to be complimented upon the effectiveness of his slides in demonstrating this point. This observation might suggest that where progesterone is used a more nearly physiologic result is obtained.

It remains important to emphasize that many patients with functional bleeding, perhaps 50 per cent, manifest spontaneous remissions and actually require no treatment. Such remissions may be induced also by curettage. Therapy which does not result in a higher cure rate has little to justify itself except perhaps a quicker control of bleeding. It may in addition be important to emphasize that, in the older age group, medical curettage should never supplant surgical curettage.

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—Briefly and to the point, I am a little disturbed over the thirty older patients who were treated as cases of dysfunctional bleeding, not having heard that all of them had the benefit of a thorough diagnostic curettage under anesthesia before treatment was instituted. I hope the essayist will reassure us on that point.

DR. HAROLD BACK, Detroit, Mich. (by invitation).—One must commend the essayist's honesty in presenting not only his successes but also his failures in attempting to induce menstruation (in the true sense of the word) from the atrophic endometrium of amenorrhea and endometrial hyperplasia as observed in instances of menometrorrhagia.

Our own experience with attempted replacement therapy in such instances of failure of ovulation are similar. As has been shown repeatedly, withdrawal bleeding can be induced in amenorrhea almost at will by estrogen or estrogen in combination with progesterone. Our studies of concomitant basal temperature determinations and pregnandiol excretion have, however, not shown any evidence of permanent curative effect from this form of therapy. Even though artificial basal temperature rises could be induced by progesterone, no evidence of ovulation could be established during or after such therapy. In several instances of secondary amenorrhea, spontaneous ovulation occurred at later dates quite independently, we believe, of our therapeutic efforts. Whatever benefits might be ascribed to such artificially induced, so-called menstruation has, we believe, purely psychic value with the additional advantage of demonstrating that the end organ is still capable of responding to suitable stimulation.

In menometrorrhagia, associated as it often is with cystic glandular hyperplasia of the endometrium, the benefit of temporary hemostasis and more orderly withdrawal bleeding is often of value. However, we believe that here too no definite curative effect can

be claimed. It is well known that endometrial hyperplasia is a manifestation of, often, only a self-limited intercurrent endocrine aberration which may be relieved spontaneously. Our own studies show no evidence of benefit to the underlying, probably pituitary factor which causes hyperestrinism from multiple follicular cyst development.

We are much interested at present in several cases under observation. The first was an instance of menometrorrhagia which had failed to respond to all accepted methods of therapy, including repeated curettage. Almost continuous menometrorrhagia since puberty was finally arrested by bilateral wedge-shaped resection of slightly enlarged microcystic ovaries. Since then, biphasic temperature patterns, pregnandiol excretion and—four months ago at the age of 28 years—the onset of pregnancy attest to the establishment of ovulation. In this instance microscopic sections of both ovaries failed to reveal any evidence of previous corpus luteum formation. We believe that ovulation had been inhibited by unopposed hyperestrinism which was relieved surgically by removal of the excessive follicular activity. We are awaiting further observations in the remaining cases before reaching conclusions.

DR. GEORGEANNA JONES, Baltimore, Md. (by invitation).—Dr. Te Linde and I have been interested in the treatment of menorrhagia with progesterone for a number of years.

I believe we are losing sight of the fact that Dr. Gray's paper is not concerned too much with the results of therapy, but with the more experimental aspects of the field. He was attempting to determine which was the best method of administration and what might be expetced from the different methods of administration of progesterone, and also to give us some information as to the underlying histology of the therapy. I am very much interested in his histologic study; it has helped me considerably.

From a clinical point of view, I would say that in the past ten years we have treated seventy-two patients. These patients were confined to the menorrhagia group and represented only seventy-two out of 700 patients with functional bleeding seen in the clinic, which gives you some idea of the frequency with which this therapy is necessary. We used it only in severe cases, in patients who are young and desire pregnancies. In this group of seventy-two patients we have 18 per cent who became pregnant. Twenty of the patients apparently were cured by therapy with no other supportive type of treatment. Everyone knows that this condition does have remissions. However, our seventy-two patients were carefully selected as to endometrial patterns, and patients with medical conditions, inflammatory conditions, or tumors were excluded. We have had no failures in therapy in this group.

I think one difficulty in therapy is that sometimes the diagnosis is not properly made. One cannot expect to have good clinical results in patients who have complicating factors or in patients who have any suggestion of secretory endometrium or a regular cycle.

One must also understand the underlying histology which Dr. Gray has shown so well. Progesterone is not hemostatic; it does not stop bleeding but only controls it in a physiologic way when given in a cyclic manner. Sometimes bleeding does not stop until seven days after withdrawal of progesterone.

DR. EMIL NOVAK, Baltimore, Md.—The fundamental disorder in most of these cases of functional bleeding and, I believe, all of the group which Dr. Gray has so intelligently discussed, is a failure of ovulation. The curative treatment would be to make the patient ovulate, but here we meet with the same difficulties encountered in trying to induce ovulation in women who are infertile because they do not ovulate. Almost all the endocrine treatments of functional bleeding which have been recommended are make-shifts in that they are surface treatments, often purely hemostatic. This, I think, is true of what I believe to be the most effective hemostatic treatment of all in functional bleeding, that with estrogens. Such treatments control the bleeding, but do not usually cure the underlying pituitary disorder. The later occurrence of ovulation is likely really to cure the patient, but this is probably more often spontaneous than endocrine-induced. Dr. Gray has

taken cognizance of these facts, since he groups his cases into those which were controlled and those which were cured. I believe it was Ambroise Paré who used to say, "I treated the patient, and God cured him." To adapt this thought to the subject of functional bleeding, we treat the patients, but most often God cures them.

DR. GRAY (Closing).—One point brought out must have a proper answer and that is Dr. Payne's question. We believe every woman with metrorrhagia after the age of twenty-five, or recurrent metrorrhagia in younger women, should be curetted under Pentothal in the hospital before hormone therapy is given.

On the other hand, patients with puberty metrorrhagia should not be curetted, since medical hormone therapy appears to control bleeding with accuracy.

Mollison, P. L., and Cutbush, M.: Exchange Transfusion in Haemolytic Disease of the Newborn, The Lancet, page 522, Oct. 2, 1948.

Whether tissue damage in the newborn is a direct effect of the circulating anti-Rh antibodies, or an indirect effect of the hemolytic process, is uncertain. While many infants with damage to the liver and brain may fail to exhibit anemia, the apparently good blood count may be due to (a) the delayed effect of a physiologic transfusion from the placenta (only counts from the cord at birth are reliable), (b) a rapid rate of red cell regeneration which may mask a high rate of hemolysis (as shown in cell survival experiments or by the hyperbilirubinemia present). Moreover, infants dying or stillborn because of profound birth anemia may not have had time to develop kernicterus. These points make it possible that tissue damage is specially associated with rapid blood destruction. The authors do not feel that anti-Rh causes direct tissue damage, since they have sometimes noted large amounts of free Rh-antibody persisting for weeks with no evidence of progressive liver or brain damage.

It is doubtful that tissue damage is established at birth, and, insofar as it may be subsequent to the destruction of Rh-positive cells, substitution transfusion is prophylactic. While either a simple or a replacement transfusion removes the physiologic stimulus (anemia) to the formation of new Rh-positive cells, the former procedure preserves the initial load of Rh-positive cells for destruction and excretion. A second rationale for exchange transfusion is the rapid correction of a profound anemia without overloading the circulation.

The authors have performed thirty exchange transfusions by the umbilical vein. (Diamond, 1947.) A transparent plastic catheter is passed 2 to 3 inches, to the point where blood is freely withdrawn. Twenty c.c. exchange aliquots are used, and the apparatus being rinsed with dilute heparin-saline solution, occasionally. The total exchange is 300 to 450 c.c., sometimes followed by a 50 c.c. donor supplement. In most cases the exchange was done within thirteen hours of birth, but the procedure has also been successful up to 38 hours after birth. There were no cases of umbilical sepsis, air embolism, or other ill effect. Prophylactic doses of penicillin are recommended, although used in only 10 per cent of the cases here reported. If some supernatant plasma-citrate is removed from the donor blood, the improved donor hematocrit permits an improved absolute and proportionate Rh-negative cell count, whereas the number of residual Rh-positive cells depends only on the volume of blood exchanged.

Analysis of this series shows a mild course in infants whose cord blood contained more than 15 mg. of hemoglobin and less than 3 mg. of bilirubin, per 100 c.c. Infants having anemia and high bilirubin had a stormy or fatal course. The authors suggest that exchange transfusion be reserved for this latter group. Of the thirty infants treated, twenty-three survived, only one showing residual nervous system damage.

IRVING L. FRANK.

Original Communications

STUDIES ON PREVENTIVE AND CURATIVE TREATMENTS FOR Rh SENSITIZATION*

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THE most recent and one of the most important advances in connection with blood transfusion is the discovery of the Rh factor. Knowledge concerning this has accumulated by leaps and bounds, and it has been necessary from time to time to revise our thinking. This, coupled with the fact that the subject is a complicated one, has led on occasion to some confusion. The essential nature of the Rh factor and its clinical applications are readily understood, if we avoid laboratory details and approach the subject from a broader and more general point of view.

A number of characteristics or factors of red cells had been discovered, and in 1937 Landsteiner and Wiener added another to the list, namely the Rh factor. All these factors, A, B, N, M, P, as well as the Rh, fall in the same general category of antigens. Antigens, under certain circumstances, have the ability to stimulate the production of corresponding antibodies. If cells containing any of these characteristics are introduced into the circulation and the corresponding antibody exists, an antigen-antibody reaction takes place and the clinical picture of hemolysis results.

Rh antibodies are not found preformed but may appear as a result of active or passive sensitization. Active sensitization may develop following repeated intravenous or subcutaneous injections of Rh-positive blood into an Rh-negative individual or as the result of pregnancy and the escape of Rh-positive cells of the fetus into the circulation of an Rh-negative mother. Passive sensitization, on the other hand, occurs if antibodies from a sensitized mother pass through the placenta into the circulation of the fetus. This paper will be limited to a report of efforts to meet the problem of active sensitization by the Rh factor.

It was most natural after scientific data concerning the nature of the Rh factor and its method of operation had accumulated that investigators should dedicate themselves to the task of preventing and counteracting Rh sensitization. In the case of transfusion this is simple. Wiener and Peters[1] recognized that 90 per cent of the post-transfusion intragroup hemolytic reactions were due to Rh sensitization. Methods of cross-matching blood of the donor with that of the patient then in vogue do not in every case detect the presence of Rh antibodies which presumably may be present. These methods must be changed. As a result such hemolytic reactions can now be avoided.

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†Director Blood and Plasma Bank, New York University-Bellevue Medical Center.

New rules have been established for the selection of donors for transfusion. Rh-positive blood should be given to all Rh-positive patients, except to newborn infants with erythroblastosis due to Rh sensitization. To these only Rh-negative blood should be transfused, even though the infant necessarily is Rh positive. Only Rh-negative blood should be given to all Rh-negative females from birth to the climacteric, otherwise sensitization by the Rh factor might follow and interfere with normal pregnancy. For Rh-negative females after the climacteric and for Rh-negative males of any age Rh-positive blood may be given when necessary providing it is recognized that as a result Rh antibodies may develop, and providing subsequently the proper pretransfusion tests are performed.[2] If sensitization results, for all subsequent transfusions only Rh-negative donors may be used. It must also be remembered that even when Rh-positive blood is used exclusively for Rh-positive patients the possibility of sensitization by the rh′ or rh″ factors may also occur.[3] This can always be avoided if a donor is selected whose Rh *type* is identical with that of the patient. The mere presence of Rh antibodies in the serum of an Rh-negative individual is inconsequential to that person unless pregnancy develops or unless transfusion is required.

Our experience has shown that while the frequency of Rh-negative individuals in the general population is about 15 per cent, demands for this type of blood for transfusion run as high as 25 and 30 per cent, and at one institution this has reached 100 per cent. This is due to the use of donors with Rh-negative blood as universal donors when preliminary Rh testing has actually been omitted. This should be condemned. The successful operation of any bank will be defeated if patients not requiring Rh-negative blood are given this variety, and if then those who genuinely require it are deprived of it. In addition it must be recognized that sensitization to the Hr factor may develop as a result of this practice and this too can interfere with a successful pregnancy.

The second circumstance during which active sensitization by the Rh factor may become apparent is during pregnancy. Levine, Burnham and Katzin[4] showed the relationship between erythroblastosis and atypical agglutinins in the mother's serum. Levine and his co-workers established the fact that at least 90 per cent of cases of erythroblastosis fetalis were due to Rh sensitization. Bloods of such mothers show the presence of Rh antibodies. Coping with the problem of sensitization due to pregnancy is not as simple as the similar problem with transfusion.

Three methods of treating the mother have been studied: (1) repeated partial replacement transfusions, (2) countersensitization with bacterial vaccines, and (3) treatment with hapten. Replacement transfusions are not really as new as they sound. As far back as 1917[5] I published my experience with an attempt to affect the course of leucemia and pernicious anemia by replacement transfusion. Recently the method has been revised. It is now used for newborn infants with erythroblastosis. Bessis of Paris is also using it for treatment of leucemia and other conditions.

It seemed reasonable that repeated partial replacement transfusions might possibly reduce the titer of antibodies in blood of a mother sensitized by the Rh factor, or at least prevent a rise. Under such circumstances a case which otherwise would be severe or even fatal might conceivably be converted into a mild one and the infant recover. To test this method four cases were treated in this fashion. All of these women had typical marital histories. They all showed Rh antibodies in their sera; two had anti-Rh agglutinins and two had Rh blocking antibodies. In one case saline agglutinins were present in a titer of 256, and in another the albumin-plasma conglutination test gave a titer of 2048. One patient was an interim case, while the other three were pregnant at the time of treatment. In each case 500 c.c. of blood were withdrawn and 500 c.c. transfused and this process repeated until the total amount previously decided upon

had been removed and replaced. In one case 6,500 c.c. were replaced over a period of twenty and one-half weeks (Fig. 1); in the second case 6,500 c.c. in eleven and one-half weeks (Fig. 2); in the third case 8,500 c.c. in nine and one-half weeks (Fig. 3); and in the fourth case 21,000 c.c. in fourteen and one-half weeks (Fig. 4). In this last case 10,000 c.c. were removed and replaced at only three sittings over a period of four days.

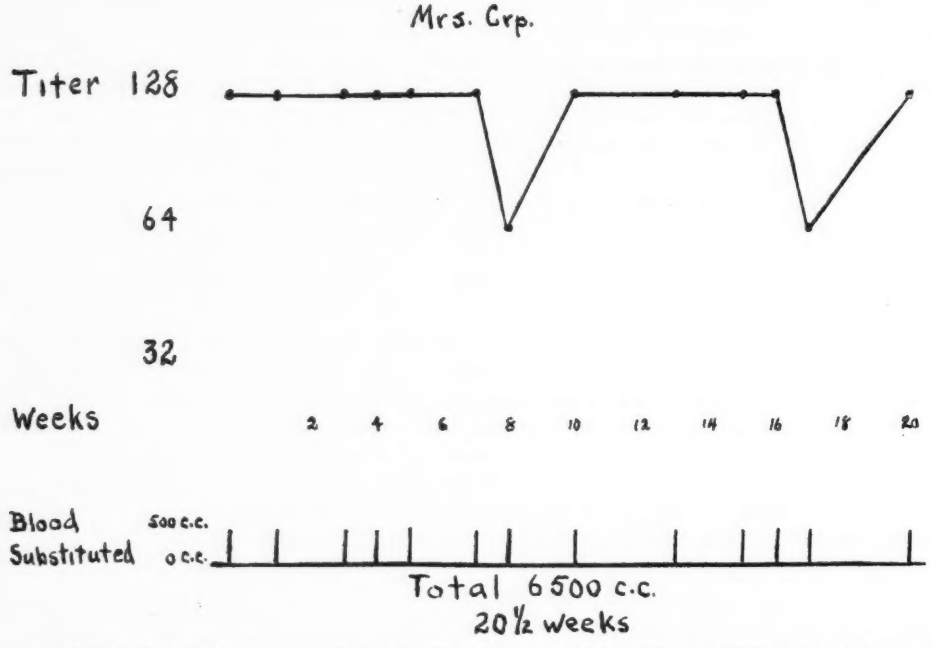

Fig. 1.—Results of antibody titrations (albumin-plasma conglutination technique) during pregnancy in Case 1 treated with replacement tranfusions. Cesarean, erythroblastotic infant.

The bloods of all patients reported in this paper were examined not only for agglutinins using saline medium, and for blocking antibodies using the indirect test, but also for antibodies using albumin-plasma medium. The illustrations throughout indicate titers obtained when the latter medium was employed. It must be remembered that a difference of one dilution between any two sets of successive titer readings, for example, the difference between 512 and 256, is of no greater significance than the difference between 2 and 1. Therefore, a scale of titers on an arithmetic rather than a geometric basis grossly exaggerates the significance of fluctuations at the upper level of the scale and is misleading. In all charts depicted in this paper the geometric scale has been used.

Figs. 1 to 4 give the results of antibody titrations in the cases where replacement transfusion was used. Because of the limitations of the test there can be a difference in the results of two successive tests of one or two dilutions which should not be interpreted as necessarily significant. If, however, repeated subsequent tests show a continuation of this downward or upward trend, the difference does become definitely significant. Although the trend in two of these cases was possibly slightly downward, in neither was it sufficiently marked to be certain that these changes were due to treatment rather than to limitations of the test.

In the first case (Fig. 1) where the titer remained unchanged throughout pregnancy, a previous pregnancy had resulted in an erythroblastotic infant who died. The present pregnancy was terminated by cesarean section after thirty-

three weeks. The infant, who was Rh-positive, was immediately given a partial replacement transfusion and made a perfect recovery. At no time was jaundice evidenced. The child is living and well and is now 1 year old. The second case (Fig. 2) was an interim case. The third patient (Fig. 3) gave birth to a 7½-month erythroblastotic infant who died within a matter of hours. The fourth patient (Fig. 4) gave birth prematurely to an Rh-negative infant who soon died.

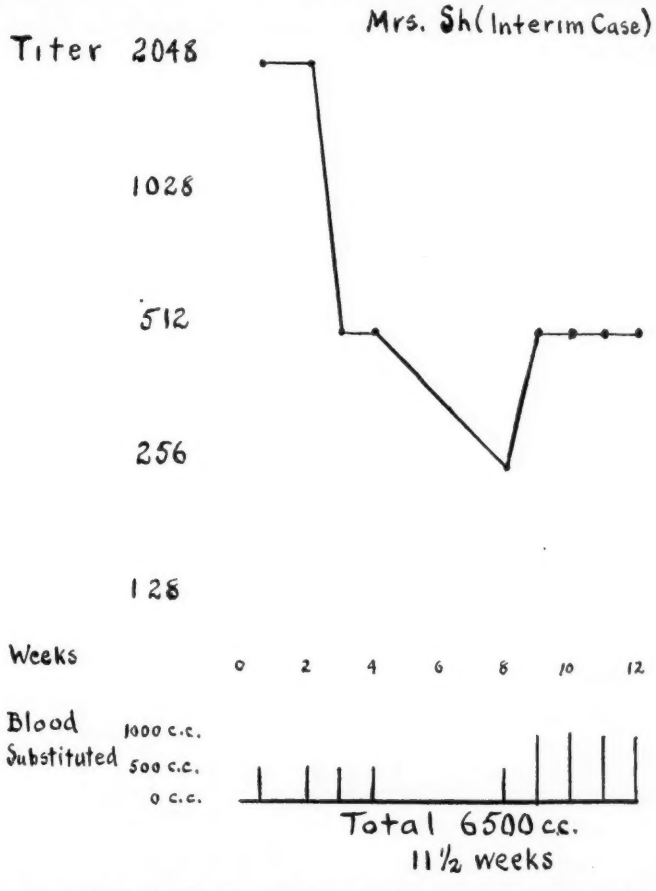

Fig. 2.—Results of antibody titrations (albumin-plasma conglutination technique) in Case 2 (not pregnant) treated with replacement transfusions.

Of course, at the outset it was fully recognized that antibodies are not only present in the circulating blood of the mother, but also that the tissues are saturated with them and that the expected results might not materialize. Beside this reserve, it is likewise possible that the rate of new production is so rapid that no appreciable reduction in titer may be observed. Perhaps the amounts of blood removed and replaced should be greater. Possibly twenty or thirty liters over the period of a week might be more effective. At present, however, I am forced to conclude that this mode of therapy in the doses used has little if any ability to reduce the titer of Rh antibodies. An additional drawback is the fact that huge amounts of Rh-negative blood are needed to carry it out. This is expensive and it might be difficult in certain localities to obtain such large amounts at a time because the patient may not be near a very large blood bank.

The second mode of therapy undertaken was that of countersensitization. As previously stated the Rh factor is an antigen. Under certain circumstances

an Rh-negative mother may develop antibodies of a specificity corresponding to that of the Rh factor inherited by her infant. The mechanism is one of antibody response to stimulation by an antigen and is identical in principle with the reaction to any other antigen.

Landsteiner[6] pointed out that specific substances have been seen to interfere with each other in their antigenic action, e.g., the highly active Forssman substance may inhibit the formation of antibodies against other specific substances. This interference, German writers have termed Konkurrenz der Antigene (competition of antigens).

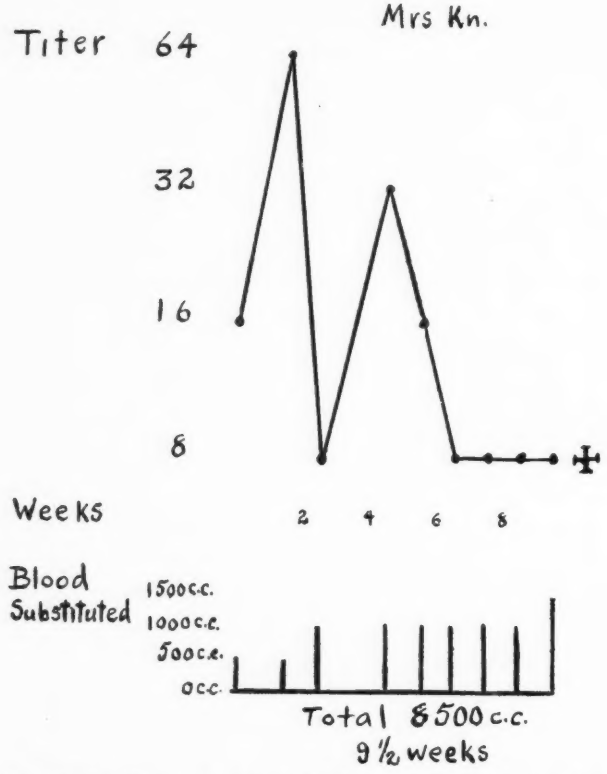

Fig. 3.—Results of antibody titrations (albumin-plasma conglutination technique) in Case 3 treated with replacement transfusions. Premature infant, erythroblastotic.

Workers in the problem of protection against viruses have had similar experiences and refer to the effect as an "interference phenomenon." Andrews[7] states that the existence of one virus in the host sometimes prevents an attack by a second virus, and the two viruses need not be antigenically related.

Another illustration of the phenomenon of competition of antigens is in connection with the use of diphtheria toxoid which contains not only diphtheria antigen, but also A substance obtained from pig stomach used for preparation of peptone necessary for production of toxoid. Therefore, when such toxoid is administered to a patient, two antigens are simultaneously injected. If the blood of the patient happens to belong to group A naturally he cannot respond to A substance and can only respond to toxoid. If he should belong to group B he is in a position to respond to both antigens and competition between the two ensue and he usually responds only to the more potent, namely, the A substance. This is supported by the findings of Tomaki and others who showed that im-

munization against diphtheria is more successful in Group A than in Group B individuals.

Additional evidence is found in a study of the incidence of Rh sensitization in pregnancy. If the mother is Rh negative, and the fetus is Rh positive, but in addition the ABO group of both mother and child are identical, only a single incompatibility exists. If in addition to the Rh incompatibility there is an ABO incompatibility, a double incompatibility exists. Both mothers may have been exposed to the identical Rh antigen, yet the incidence of Rh sensitization in these two groups of pregnancies differs. According to Diamond (personal communication) if the husband is homozygous and there is a single incompatibility, the incidence of sensitization is 11 per cent, whereas if there is a double incompatibility, the incidence of sensitization is reduced to 4 or 5 per cent.

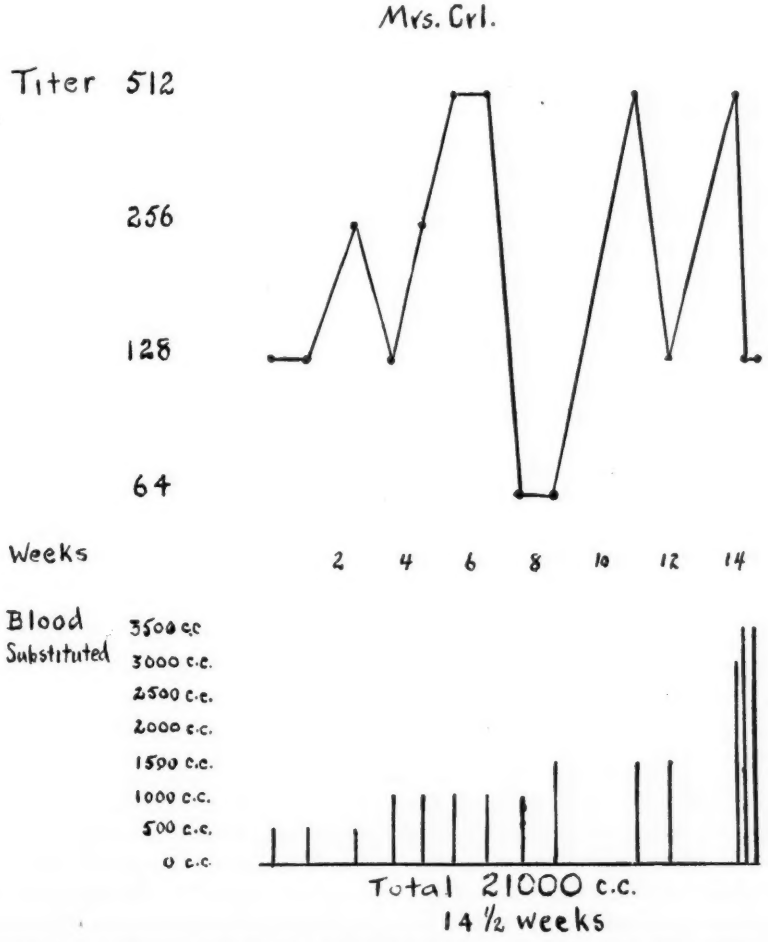

Fig. 4.—Results of antibody titrations (albumin-plasma conglutination technique) in Case 4 treated with replacement transfusions.

Under similar conditions with a heterozygous husband and a single incompatibility, the incidence is 3 per cent, whereas with a double incompatibility it is reduced to 1 per cent. Levine,[8] Wiener,[9] as well as Race[10] and his co-workers have also made similar observations. A plausible explanation for these findings is that with a double incompatibility the A or B factor is in competition with the Rh factor. The A and B factors are more antigenic than Rh, and the

mother tends to respond to them with greater ease than to the Rh factor which is then ignored.

Competition of antigens is merely a special situation illustrating a general physiologic phenomenon; namely, that a strong stimulus tends to suppress a weak one. It is difficult to hear a whisper in a boiler factory, or to detect faint odors in the presence of stronger odors, or to feel deeper seated pain when counterirritation is applied. This does not mean that the body is incapable of responding to more than one stimulus or one antigen at the same time, but merely that injection of a strong antigen *tends* to suppress the antigenicity of a weaker one injected at the same time. For competition of antigens to operate, correct "timing" is of utmost importance. To use a prosaic example, a loud noise today cannot overwhelm a whisper uttered tomorrow. Similarly, if the two antigens are not present in the individual at the same time, they can hardly compete with one another. Under natural conditions, when there is a passage of fetal blood into the maternal circulation, the same blood cells carry A and B antigens as well as Rh antigen so that in this instance timing is perfect, and interference results.

There is much evidence to support the theory of competition of antigens. Wiener[11] was the first to suggest that this phenomenon might be put to practical use and result in protection of Rh-negative women carrying Rh-positive fetuses, and that innocuous antigens such as typhoid and pertussis vaccines can be used to suppress the antigenicity of the Rh factor. There have been differences of opinion on the subject, yet none has been based on a large practical trial. The subject seemed to be of such great importance that a systematic study was undertaken. Methods for the production of diagnostic sera offered an opportunity to test the theory. At first diagnostic sera for Rh studies were prepared by artificial sensitization of animals. This for many reasons was unsatisfactory. Subsequently, sera obtained from mothers of erythroblastotic infants were used for this purpose. However, demand for diagnostic sera became so great that more recently workers in this field have obtained diagnostic serum from volunteer male professional donors injected with Rh-positive blood. Of a group of nine injected donors reported by Wiener and Gordon[12] five, or 55 per cent, responded with the production of Rh antibodies. Wiener also states in a personal communication that he has now increased this group to forty-seven. Of these, 38.3 per cent developed antibodies after the second injection. Twenty-three of the remainder received a third injection of Rh-positive cells and six developed antibodies. The cumulative total per cent sensitized, therefore, after two or three injections, was 54.4 per cent. This is further supported by a report of Diamond who states that in a group of 380 male Rh-negative veterans given Rh-positive blood transfusions, 53 per cent developed Rh antibodies. By reproducing Wiener's exact procedure, but with the addition of vaccine therapy, Wiener's series of injected donors could be used as my control series. This offered the opportunity to determine the preventive value of countersensitization. The program was planned to simulate first, second, and even third pregnancies, during which vaccine was administered. Of seven injected Rh-negative men only one developed antibodies, an incidence of about 14 per cent (Table I) instead of the expected 54.4 per cent. It is fully recognized that conclusions based on small numbers might be erroneous and that absolute safety is found only in very large numbers. Yet large numbers in a test of this sort are from a practical standpoint difficult of attainment and hardly feasible. At any rate the results certainly are very suggestive. Another observation is that the only individual of this group who did develop Rh antibodies showed a negative Widal to the O antigen although positive to the H antigen, whereas all other donors injected with typhoid vaccine who developed no Rh antibodies responded positively to both typhoid antigens.

TABLE I. OBSERVATIONS ON Rh SENSITIZATION IN Rh-NEGATIVE MALES WITH AND WITHOUT COUNTERSENSITIZING VACCINE INJECTIONS

INVESTIGATOR	COUNTER-SENSITIZATION	NUMBER OF INJECTIONS OF Rh-POSITIVE CELLS	NUMBER OF SUBJECTS	FREQUENCY OF Rh ANTIBODY FORMATION		CUMULATIVE TOTAL (PER CENT) SENSITIZED
				NUMBER	PER CENT	
Present study	Typhoid and pertussis vaccine used	2	7	1	14	14
		3	5	0	0	14
Wiener* (control series)	None used	2	47	18	38.3	38.3
		3	23	6	26.1	54.4

*Proc. Soc. Exper. Biol. & Med. 70: 576, 1949.

Van Loghem[13] of Holland has reported the results of Rh sensitization of volunteer donors. He believed that the injection of vaccine simultaneously with exposure to the Rh factor will increase the incidence of those who produce Rh antibodies. His conclusions, however, are open to question, because his donors received numerous injections of Rh-positive cells without vaccine, and then later received repeated injections (totaling up to sixty and more) of Rh-positive cells and only a few injections of vaccine. His donors first had been "primed" by the Rh antigen and then later given stimulating doses of Rh-positive cells. Even then, his incidence of sensitization was 21 per cent which is much lower than the expected 54.4 per cent. His technique was entirely different from the one followed in this present test and, therefore, his results and those of this study are not comparable. In my series, as well as in Wiener's, between each injection of cells there was an interval of 90 or more days, and the technique followed in both investigations was identical in every respect except that in my series weekly injections of vaccine (totaling twenty-one to twenty-seven) were administered to prevent Rh sensitization.

Another possibility that has been claimed is that of nonspecific response. It has been suggested that if an individual has already been "primed" by the Rh factor, subsequent injections of vaccine might stimulate the production of Rh antibodies.

Because of the experimental evidence supporting the theory of competition of antigens, and because of the lack of danger in connection with the use of typhoid and pertussis vaccines, and because any immunity developed by the mother would be of value to the infant, a clinical trial was begun two years ago.* The following program is now being carried out in the outpatient Obstetrical Department of St. Clare's Hospital.† Rh typing is performed on the blood of every expectant mother. In other words, her blood is examined not only for the Rh_0, but also for the rh′, rh″ and hr′ factors. In addition an ABO grouping, and M and N typing is made. If the mother is found to be Rh negative, whenever it is possible to obtain blood of the patient's husband, similar examinations are made. If these tests reveal that the possibility of sensitization exists, countersensitization is begun. Typhoid vaccine 1,000 million per cubic centimeter and pertussis vaccine 20,000 million per cubic centimeter furnished by the Department of Health of the City of New York are used. Until pregnancy is terminated alternating series of six weekly injections of each of these vaccines are given. The dose is gradually increased at the beginning of each series. If an injection is followed by a reaction, the subsequent dose is cut in half. Monthly, up to the seventh month, examinations for anti-Rh agglutinins and Rh blocking antibodies are made. During the seventh month this is done twice and then once a week

*These cases were kindly referred to me by Dr. Locke Mackenzie.

†The opportunity to introduce this program was kindly afforded me by Dr. Michael Jordan, the attending obstetrician.

until the end of pregnancy. An Rh typing is done on the cord blood of the newborn infant. It is also examined for antibodies and coating of the cells. Since this program entails a terrific amount of work and cooperation, it was not always possible to carry out every detail as outlined. At the obstetrical clinic of Woman's Hospital I have introduced a similar program, except that no vaccine is being given. This might be used as a control group, except that the two groups of patients are racially different.

Up to the present we have treated or are still treating by countersensitization ninety-three Rh-negative women (Table II). Even though it is recognized that the first pregnancy is practically always spared, twenty-six of the group who were primiparas were also given treatment because of the importance of "priming." It is felt that they should be "primed" against the bacterial antigen before they have the opportunity to be "primed" against the Rh antigen, thus making certain that the vaccine is the more potent antigen. It also seems important that these primiparas be given an injection of vaccine at the time of delivery when the likelihood of leakage of Rh-positive cells from the fetus is probably greatest. It is hoped that they will return at the time of their second pregnancy so that this thesis can be tested. Fifty-eight of the patients were multiparas. Of the entire group, one patient, in spite of countersensitization, developed Rh antibodies. Peculiarly enough her Wassermann was four plus. The significance of this is unknown. After the birth of her infant a partial replacement transfusion was performed. A mild degree of jaundice developed. However, the child recovered without any further treatment and is now living and well.

TABLE II. OBSERVATIONS ON Rh SENSITIZATION DURING PREGNANCY IN Rh-NEGATIVE PATIENTS RECEIVING COUNTERSENSITIZING VACCINE INJECTIONS

	NUMBER OF Rh-NEGATIVE WOMEN TREATED	RESULTS OF PREGNANCY			
		STILL-BIRTH	ERYTHROBLASTOSIS		NORMAL
			DIED	RECOVERED	
Nonsensitized primiparas	26*	0	0	0	25
Nonsensitized multiparas	58†	0	0	1	40
Previously sensitized multiparas	9	5	1	3	0

*One of these pregnancies is not yet terminated.
†Seventeen of these pregnancies are not yet terminated.

Nine women who had been sensitized by previous pregnancies were also treated. This practice has now been discontinued. Our experience shows that vaccine therapy in such women is of no avail. If the value of vaccine therapy can definitely be established it will be as a *preventive* measure for those who still show no evidence of sensitization. Although it is felt that sufficient evidence has accumulated to warrant the belief that this form of therapy may possibly prove to be of value to reduce the incidence of sensitization to the Rh factor, it is definitely not infallible. It is also fully recognized that it will take experience of several years more before a final appraisal of this prophylactic treatment can be given. In making use of this therapy one must keep in mind the necessity for proper "priming" and proper "timing," otherwise failures will result. "Priming" is necessary to insure the greater potency for the vaccine as compared to the Rh factor. "Timing" is necessary to develop competition between them. If a patient has previously been sensitized by the Rh factor, it may have become a more potent antigen than the vaccine. The vaccine treatment must be continuous throughout pregnancy. Perhaps some other antigen will be developed or used which can be given less frequently, and that it will be so retained by the patient that the effect will be more continuous and solve the problem of

"timing." That such vaccines may be feasible follows from experimental work of Freund and his co-workers[14] on bacterial vaccines suspended in oil of light viscosity.

It will probably take several years before the final word on this subject is spoken, especially if only one or two investigators carry out the work. This is true because only a small percentage of women in whom the potentialities for sensitization exist become sensitized. I estimate that it will be necessary to observe at least approximately 10.000 consecutive pregnancies to arrive at a final answer. Perhaps even double this number may be necessary. If this method of treatment then shows a definite reduction in the incidence of erythroblastosis, a final conclusion could be arrived at. Obviously this would be a colossal undertaking. It is suggested, therefore, that this treatment be undertaken by other clinics and that results be pooled and evaluated. It is only in this way that we can more quickly come to a definite decision. It is necessary to have very large numbers of cases treated in order finally to say exactly what role the treatment has played in the reduction of the incidence of erythroblastosis fetalis.

The third method of approach studied was the use of a new substance, the so-called hapten. The term hapten was introduced by Landsteiner to designate materials capable of reacting specifically with antibodies in vitro, but incapable themselves of stimulating the production of antibodies when injected into experimental animals. Rh hapten is intended for treatment of women whose blood shows the presence of Rh antibodies and for treatment of infants with erythroblastosis.

In 1944 Wiener[15] suggested the possible value of hapten. More recently Carter[16] produced hapten and used it clinically. This substance she obtains from an ethereal extract of Rh-positive cells which is next reduced to dryness, and the residue dissolved in alcohol. She then assays it for potency by two methods, complement fixation and direct inhibition of agglutinins, and administers it by intramuscular injection. According to Carter, Rh hapten appears to be a lipid substance which does not produce antibodies when injected into the experimental animal.

If a substance can really be prepared which can eliminate or reduce a sensitized person's Rh antibody titer this would obviously be of great value in the antenatal prevention of erythroblastosis. Carter has reported results of treatment with Rh hapten in a series of sensitized Rh-negative women, as well as a series of infants with erythroblastosis. Her report claims excellent results.

Again because of the importance of the subject, and the interest that Carter's report has aroused, preparation and assay of Rh hapten according to her technique and a study of its effects on patients were undertaken by me at the Blood Bank of the New York University-Bellevue Medical Center, formerly the New York Post-Graduate Medical School and Hospital. To be certain that there could be no question about the potency of the hapten used in these trials, most of the material used was either prepared by and furnished to me by Carter, or prepared at my laboratory and found satisfactory when assayed by her. Up to the present we ourselves have been unable to our satisfaction to confirm Carter's assay findings, although we have used the Kolmer complement fixation test and the direct inhibition of agglutinins as recommended by her. We have also tried the quantitative complement fixation method as applied by the New York State Department of Health for serologic diagnosis of syphilis. In some lots we have found evidence of fixation of complement but only in very low titer and of questionable specificity, even though when this same material was submitted to Carter's laboratory her report stated that it was potent and satisfactory. In most lots we have found no evidence of complement fixation. By the method of direct inhibition of agglutinins we have found little if any

effect. Here again we could not convince ourselves of its specificity; the reactions with anti-A and anti-B sera were similar to those with anti-Rh serum, suggesting that the effect was due to the alcohol or other nonspecific materials in the extract.

TABLE III. RESULTS OF TREATMENT WITH Rh HAPTEN

INJECTIONS HAPTEN			Rh ANTIBODY
NO.	INTERVAL (DAYS)	DOSE (MG.)	TITER
CASE 1 (PREGNANCY)			
1	0	200	128
2	7	200	256
3	7	200	256
4	7	200	256
5	7	200	192
Result: Premature Rh-negative infant. Died within a few hours.			
CASE 2 (PREGNANCY)			
1	0	1M*	250
2	4	1M*	320
3	16	1M*	320
4	5	1M*	320
5	19	200*	320
–	3	–	320
Result: Normal Rh-negative infant. W. injections given and titrations done by Dr. A. S. Wiener.			
CASE 3 (NOT PREGNANT)			
1	0	1M*	24
2	14	1M*	8
3	14	1M*	12
4	14	1M*	12
5	14	1M*	8
6	7	100	8
7	7	200	8
8	7	200	8
9	1	200	–
10	1	200	4
11	1	200	–
12	1	200	8
13	3	200	4
14	3	200	8
15	1	200	4
16	3	–	8
CASE 4 (PREGNANCY)			
1	0	1M*	4
2	6	200	4
3	8	200	4
4	7	200	4
5	7	200	2
6	5	200	4
7	1	200	3
Result: Erythroblastotic infant. Replacement transfusion. Living and well.			
CASE 5 (PREGNANCY)			
1	0	200	6
2	7	200	16
3	7	200	16
4	7	200	32
5	7	200	24
6	1	200	–
7	1	200	–
8	2	200	32
Result: Erythroblastotic twins. Replacement transfusions. Living and well.			

TABLE III—CONT'D

INJECTIONS HAPTEN			Rh ANTIBODY TITER
NO.	INTERVAL (DAYS)	DOSE (MG.)	
CASE 6 (NOT PREGNANT)			
1	0	200	48
2	5	200	48
3	5	200	96
4	7	200	32
5	7	200	48
6	7	200	64
7	7	200	96
8	7	400§	48
9	7	400§	64
10	7	200	64
11	7	400§	64
12	7	800§	32
13	7	600§	128
14	7	400§	128
15	7	400§	128
CASE 7 (INTERIM)			
1	0	200	512
2	5	200	256
3	7	200	256
4	7	200	256
5	8	200	256
6	6	200	384
7	7	200	256
8	7	200§	384
9	7	200§	512
10	7	400	384
11	7	400§	384
12	7	600§	384
13	7	600§	768
14	7	400§	–
15	7	400§	512
CASE 8 (PREGNANCY)			
1	0	200	16
2	7	200§	16
3	7	400	32
4	7	600	16
5	7	800	8
6	7	600§	32
7	7	400§	32
8	7	400§	16
9	7	400§	32
10	7	200§	32
11	7	200§	32
12	7	200§	32
13	7	200§	32
14	7	200§	32
15	7	200§	32
16	7	200§	32
17	7	200§	32
18	7	200§	24

Result: Macerated stillborn fetus. In this case and in Case 11 antibody titrations on identical specimens were carried out not only by our laboratory but also by that of Dr. Philip Levine with comparable results.

TABLE III—CONT'D

INJECTIONS HAPTEN			Rh ANTIBODY TITER
NO.	INTERVAL (DAYS)	DOSE (MG.)	
CASE 9 (NOT PREGNANT)			
1	0	200	64
2	6	200	64
3	7	200	64
4	7	200	96
5	7	200	96
6	4	200	64
7	3	200§	32
8	4	200§	48
9	3	200§	64
10	4	600§	64
11	3	600§	48
12	4	–	64
CASE 10 (NOT PREGNANT)			
1	0	200	32
2	7	200	32
3	7	200	64
4	4	200	48
5	5	200	32
6	2	200	64
7	4	200	48
8	3	200	64
9	4	200	48
10	3	200§	32
11	3	200§	64
12	4	400§	64
13	3	600§	48
14	4	600§	64
15	3	600	32
16	4		64
CASE 11 (NOT PREGNANT)			
1	0	1M*	64
2	7	200*	128
3	7	200*	64
4	7	200	64
5	7	200	64
6	7	200	64
7	4	200†	32
8	2	200†	64
9	4	200†	32
10	3	200	96
11	4	100‡	64
12	3	200	128
13	4	400	32
14	3	200	64
15	4	400	96
16	30	500‡	64

M, 1,000 units.

*Hapten prepared by and assayed by Mrs. Carter. A second source of hapten was that used for all injections without *any* symbol following the dosage in milligrams. This was prepared by our laboratory but assayed by Carter and declared satisfactory.

†Hapten obtained from a third source.

‡Hapten obtained from a fourth source.

§Material not assayed by Carter but prepared at our laboratory.

However, since the material is apparently harmless and since approved material was available, it was used for clinical trial. Table III gives a summary of the results of treatment with Rh hapten in eleven patients to whom a total of 130 injections were given. Fourteen injections were of hapten prepared and assayed by Carter. Five injections were of hapten obtained from two other sources. Seventy-three injections were of hapten prepared by us but assayed by Carter and declared satisfactory by her. Thirty-eight injections were of hapten prepared by us but not submitted to her for assay. Each patient received from five to eighteen injections. The time interval between most injections was seven days, although, as can be seen from Table III, this in certain instances was reduced to twice a week and even daily. The dose of most injections was 200 mg., but in some cases when no favorable effects were evident the dose was increased to 400, 600, and 800 mg.

In only one patient (Table III, Case 3) was there a decline in titer values, and this was slight in degree. In a second case (Table III, Case 5) there was a slight rise, while in the other nine cases there was no evidence of any ability on the part of Rh hapten, irrespective of the source, the dosage, or the frequency of administration, appreciably to change the titer of Rh antibodies in the blood of these sensitized women.

Six of the women treated were interim cases and five were pregnant. They all had typical marital histories. They all showed in their sera anti-Rh agglutinins, Rh_0 blocking antibodies, or both. They all had previously given birth to erythroblastotic children, stillborn children, or both. Of the five treated during pregnancy, one gave birth to a premature Rh-negative infant who died within a few hours. The second gave birth to a normal Rh-negative infant. The third was delivered of a macerated stillborn fetus. The fourth gave birth to an erythroblastotic infant, and the fifth gave birth to erythroblastotic twins. These three infants with erythroblastosis received exchange transfusions and are living and well.

Summary and Conclusions

All of our attempts to date to reduce or eliminate Rh antibodies in the sera of Rh-negative women *already sensitized* to the Rh factor have been of little or no avail. Four women sensitized by the Rh factor were treated with exchange transfusions. However, in no case was there an appreciable change in the Rh antibody titer despite the use of enormous amounts of Rh-negative blood. Our results have also been negative when we used the so-called hapten as advocated by Carter. To test this material thoroughly 130 injections were given to eleven patients without appreciable effect. At the present time the only recourse open to luckless couples where the degree of Rh sensitization is extreme is to adopt a child or to resort to artificial insemination from an Rh-negative donor, or, if the husband is heterozygous, to take their chances that the next baby might prove to be Rh negative. In cases where the degree of sensitization is mild, it may be possible to save the baby by inducing labor prematurely and then by giving the infant, without delay, an exchange transfusion.

Obviously, the best results would be obtained if successful efforts could be made *to prevent Rh-negative women from becoming sensitized in the first place.* Eugenic marriages have been suggested but are impracticable. For the *prevention of sensitization* our results suggest that the proper application of countersensitization with harmless vaccines may possibly reduce the chances of Rh sensitization following the birth of an Rh-positive child. However, further experience with this procedure is necessary before a final conclusion can be drawn. Difficulties of proper "priming" and "timing" in applying such

treatment make it advisable that it be used only under carefully controlled conditions until adequate statistical data are compiled. Vaccines should be prepared so that less frequent injections are necessary. Any therapy proposed for these patients should be tested critically and thoroughly evaluated, but with an open mind. In any event, during the developmental stage of any procedure one must be very conservative and be careful not to arouse false hopes in the minds of these unfortunate couples.

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Tumors that obstruct the birth canal in pregnancy usually arise from the reproductive system, such as uterine fibromas and ovarian tumors, but in the case reported the tumor was extragenital. The patient in this case was twenty-four years of age when admitted to the Mayo Clinic. Eight months previously a pelvic tumor had been palpated at the time of a routine examination; at that time it caused no symptoms. Surgical exploration of the pelvis showed the tumor to be retroperitoneal and it was not removed. At the time of admission to the Clinic, a diagnosis of pregnancy of about three months was made. The uterus was retroverted and there was a firm mass anterior to the uterus that appeared to be fixed posteriorly to the sacrum. Operation was done for removal of the tumor without interruption of the pregnancy. On microscopic examination the tumor was found to be neurofibroma; no signs of other neurofibromas were found. This case is of interest to the obstetrician because incarceration of the uterus by the tumor or by adhesions might produce abortion; or, if the pregnancy went to term, the tumor would cause a serious impediment at the time of labor producing dystocia. Presacral tumors are rare, but routine physical examination and adequate prenatal care are necessary in case such a tumor complicates pregnancy, in order to prevent obstetric complications and needless operations. HARVEY B. MATTHEWS.

PLACENTA ACCRETA COMPLICATED BY HEMOPERITONEUM

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PLACENTA accreta is defined as that pathologic condition in which the chorionic villi are in direct contact with and are interspersed among the actual muscle bundles of the myometrium. There is a deficiency of decidual tissue resulting in a partial or complete absence of this important structure. Attempts at separating such a placenta can lead only to tearing of the uterine wall itself, as there is no line of cleavage between the placenta and muscle.

The incidence of placenta accreta in different clinics varies widely from: The Boston Lying-in Hospital, 1 in 1,956 deliveries to 1 in 17,464 deliveries at the Baltimore City Hospitals. Irving and Hertig stress the fact that cases of partial placenta accreta are often overlooked and are spoken of as densely adherent placentas. The tissues removed should always be examined microscopically when any difficulty is encountered in manually removing a placenta.

There are at least 163 cases of placenta accreta reported in the literature to date, in which the diagnosis has been proved by microscopic examination. The case of placenta percreta reported below is remarkable in that it was complicated by massive hemoperitoneum in the absence of gross rupture of the uterine wall. The vaginal bleeding was minimal and the hemorrhage occurred into the peritoneal cavity from rupture of large subserosal veins.

The patient was a 24-year-old, white para 0, gravida ii. Her first pregnancy had ended in a spontaneous incomplete abortion at about six weeks with severe hemorrhage. She gave a history of having had a curettage, blood transfusion, and a febrile but eventually complete convalescence.

She became pregnant again six months after this septic illness. Her local physician treated her during the first five months for severe nausea and vomiting and irregular vaginal bleeding. She had no unusual complaints when seen by one of us (M. D. P.) six weeks before her calculated date of delivery. She appeared pale, undernourished, with very poor general hygiene, but her pulse rate, blood pressure, urinalysis, and abdominal examination were normal at that visit. Two weeks later she was admitted to the Albany Hospital with mild irregular uterine contractions. The abdomen was tender to the touch but she did not localize the tenderness. The cervix was a finger tip dilated and the fetal heart rate was recorded as 140 per minute. Her symptoms subsided promptly after a night's sleep and mild sedation. A second admission for apparent false labor with similar findings but intensified pain occurred one week after the first and she was again sent home. She returned twenty-four hours later appearing acutely ill.

On this third admission, the uterine contractions were intermittent and the fetal heart was definitely heard. No vaginal bleeding was seen. Very striking were the extreme and increasing pallor, the pinched expression of the face, and the rising pulse rate. The abdomen was tense, tympanitic in its upper half, but there was still no localization of tenderness or palpable abnormality of the uterus. The cervix was still a finger tip dilated.

A blood count revealed 1,780,000 red cells with 4.5 Gm. (31 per cent) of hemoglobin. Compatible blood was obtained and transfusion started. The urine showed a trace of

glucose and bile, was negative for albumin, acetone, and diacetic acid. The blood pressure averaged 140/70 before the onset of true labor which began during the transfusion.

There was no external bleeding. The pulse rate rose to 170 per minute and the systolic blood pressure fell to about 80. Abdominal palpation revealed nothing to support a diagnosis of uterine rupture although the general picture was that of hemorrhage. Labor proceeded rapidly and a 6-pound stillborn fetus was delivered easily by the breech under cyclopropane-oxygen anesthesia. Plasma and whole blood were kept running into her veins while separation of the placenta was awaited. A moderate amount of vaginal bleeding was then noted. Since further blood loss was to be avoided, an attempt was made to remove the placenta manually. No line of cleavage was palpable and the exploring fingers went deeply into the myometrium. It was obvious that the placenta would not come free without tearing the uterine wall. The uterus was therefore tightly packed with gauze and the patient returned to bed. Her general condition was so poor that an attempt was made to improve it before hysterectomy was done. She was given repeated transfusions and oxygen by nasal catheter. She had a severe reaction to one transfusion so that three days elapsed before the laparotomy was performed.

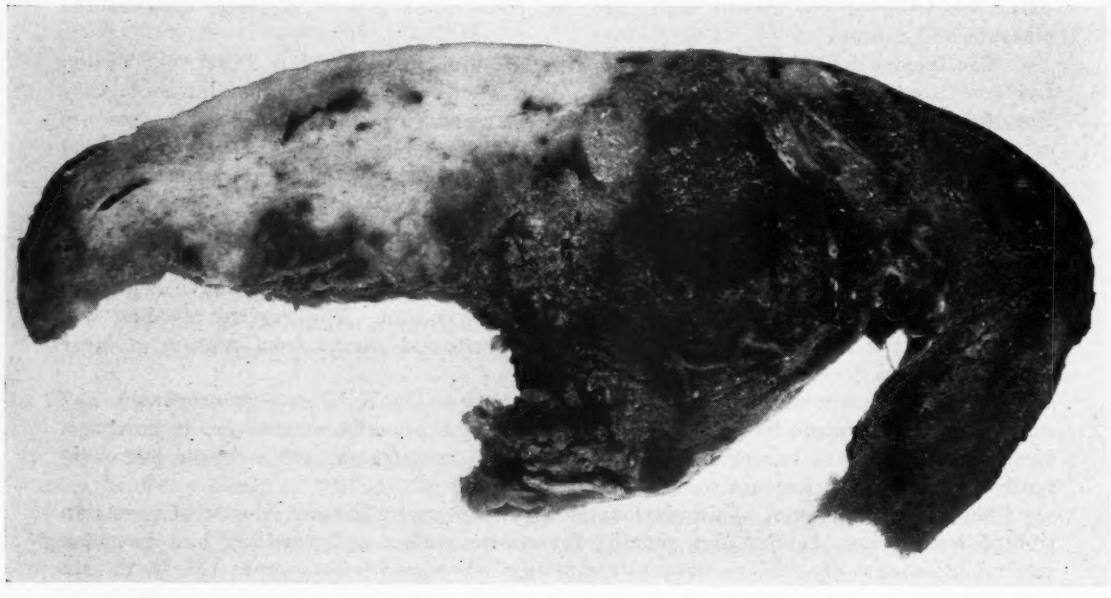

Fig. 1.—A sagittal section through the center of the placental site and the anterior uterine wall shows the rather abrupt transition between intact and invaded myometrium. The upper half of the anterior wall is replaced by intact chorionic villi. Diffuse subserosal hemorrhage is present in the region of the fundus. Thrombosis of many of the myometrial veins and the placental sinusoids is evident. A ragged necrotic membrane is attached to the endometrial surface below the placental attachment, in the region of the decidua vera. (×4/5.)

Under cyclopropane-oxygen anesthesia, the peritoneal cavity was entered and 1,500 c.c. of blood were removed by suction. An unmeasured amount of free blood was left in the peritoneal cavity. The uterus presented a most unusual picture; the right cornu and the top of the fundus were replaced by a spongy purplish mass. This mass was covered by serosa and many large dilated veins. The omentum was not attached to the fundus but had fragments of organizing blood clot attached to its lower margin. This indicated that the omentum had attempted to plug the bleeding area but had been torn loose during the severe uterine contractions incident to labor. The spongy mass had the appearance of placental tissue. The possibility of chorionepithelioma could not be disproved grossly. Cystic ovaries and a secondary mass in the left broad ligament supported this theory.

Therefore, the uterus, both Fallopian tubes and ovaries, and the broad ligament mass were removed. As soon as the bleeding was controlled, the patient's condition improved rapidly. Transfusion was given during the operation and postoperatively. Sulfathiazole powder was sprinkled liberally in the peritoneal cavity and later given by mouth. She had an amazingly calm convalescence and is well five years postoperatively.

Surgical Specimen.—A full-term postpartum uterus, with both ovaries and Fallopian tubes attached, showed a large, roughly circular zone of subserosal hemorrhage in the fundus with a jagged linear zone of erosion in the serosa. On section of the uterus, the upper one-third of the uterine wall was replaced by placental tissue (Fig. 1). The zone of transition between normal and invaded myometrium was sharp and distinct. The ovaries contained numerous follicular cysts and a large well-preserved corpus luteum of pregnancy.

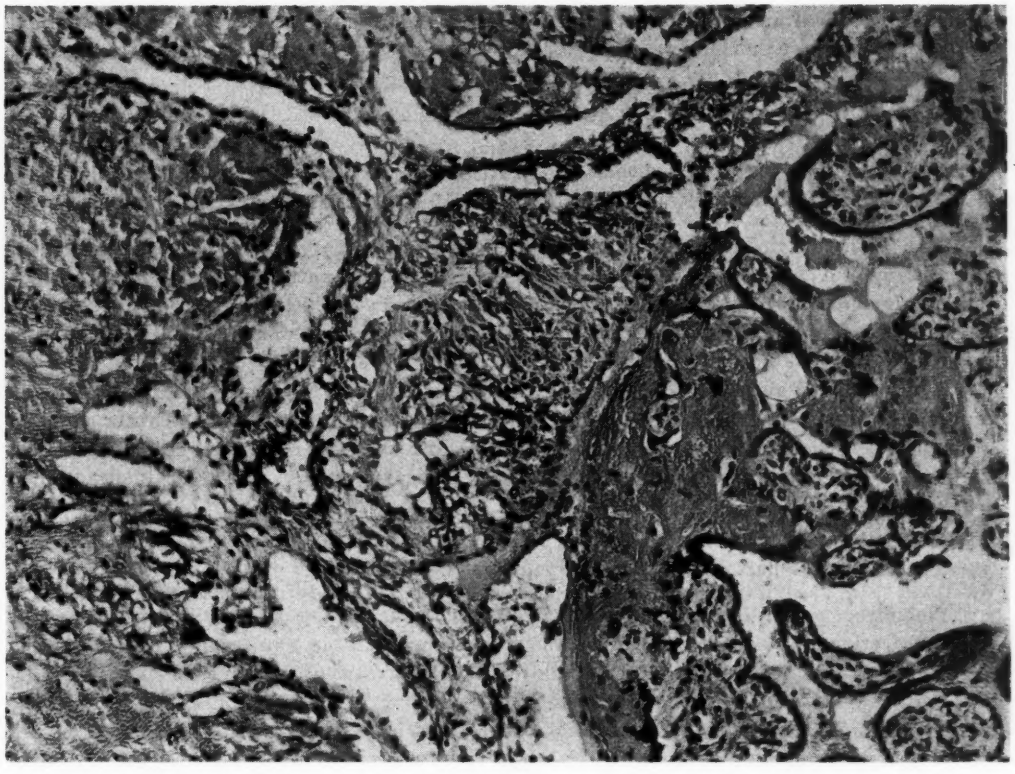

Fig. 2.—A high-power view is seen of the area of placental attachment. Chorionic villi and trophoblastic epithelial cells are in direct contact with partially necrotic and acutely inflamed myometrium, with no interposition of any decidual tissue. (×165.)

Microscopic Description.—A section through the anterior uterine wall revealed replacement of myometrium by chorionic villi. The villi, and in some situations isolated trophoblastic cells, lay directly on the myometrial cells (Fig. 2). Nowhere were any decidual elements seen. The fibrin stria of Nitabuch, usually associated with the decidua, was absent. The stria of Rohr was imperfectly formed and ill defined.

The left broad ligament mass proved to be composed of recent and organized blood clots. No tumor tissue was seen.

Final Diagnosis.—Placenta accreta with rupture of subserosal veins and hemoperitoneum; organizing and recent hematomata of the left broad ligament; follicular cysts of ovaries; corpus luteum of pregnancy.

Comment

In view of the varied etiology, it is probable that in each case of accreta more than one cause could be important. The instance described in this report can most reasonably be attributed to previous endometrial damage following postabortal sepsis. There was complete absence of decidual tissue at the placental site. Also in the areas away from the placental site, which should have showed decidua vera, cells of decidual origin were not identified.

Conclusion

As far as could be ascertanied from the literature, hemoperitoneum complicating placenta accreta in the absence of gross rupture of the uterus has not been described heretofore. The bleeding into the peritoneal cavity was caused by rupture of a large subserosal myometrial vein.

Whatever the cause of placenta accreta, it is safe to say that its presence constitutes a major obstetrical emergency. Abdominal hysterectomy is statistically the safest method of treatment, where hemorrhage is present, especially if attempts at manual extraction have been kept at a minimum.

Brendemoen, O. J., and Brendemoen, C.: Anti-A and Anti-B Isoagglutinin Titers in Rh-Immunized Pregnant Women, J. Lab. & Clin. Med. 33: 1089, Sept., 1948.

The authors briefly review the literature concerning the problem of relationship between Rh and A or B immunization. They investigated 87 anti-Rh containing sera which were obtained among 25,000 samples drawn from patients in the last two months of pregnancy. As controls, 100 sera from Rh-negative nonimmunized pregnant women and 100 sera from Rh-positive pregnant women were used.

They obtained significantly lower anti-B titers in A and O blood of Rh-negative patients who had Rh antibody than in the control groups. The anti-A titers did not differ notably. A simple negative correlation between anti-B and anti-D titers could not be demonstrated. The general ABO and MN distribution was within normal limits. S. B. GUSBERG, M.D.

Salvin, Monte: Uterotubal Insufflation With Penicillin and Streptomycin Aerosols. A Preliminary Report, West. J. Surg., page 500, Sept., 1948.

Nebulized penicillin and streptomycin for introducing the antibiotic directly to the site of infection was an outcome of techniques designed for the treatment of gas casualties in World War II. The idea has been employed for the treatment of pelvic inflammatory disease, utilizing the technique of uterotubal insufflation. A DeVilbiss nebulizer is attached to the insufflation apparatus and charged with 500,000 units of penicillin.

Prophylaxis against infection in the routine performance of the Rubin test has prompted the author to use the penicillin aerosol routinely in performing these tests. As a therapeutic procedure, the method requires further study, but the results thus far are encouraging.

WILLIAM BICKERS.

THE VAGINAL SMEAR. "PRECANCER" CELL STUDIES USING A MODIFIED TECHNIQUE*

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IN MANY major advances in the history of medicine, the original discovery preceded practical use by several years. Fleming's discovery of penicillin, lay dormant in the research laboratories for ten years before its epoch-making significance became realized. The bactericidal properties of sulfanilamide were recognized by Heidelberger at the Rockefeller Institute as early as 1916. Similarly, for all we know, the cause and cure of cancer may be discovered ten years before our inadequate vision may register its true significance. One of the major advances of recent years in the cancer field followed this same pattern. It is now over twenty years since Papanicolaou[1] first reported finding cancer cells in human vaginal secretions. Only now are we beginning to utilize this most valuable diagnostic procedure for the saving of human lives.

The Papanicolaou techniques are having even more far-reaching applications to cancer diagnosis in the discovery by similar principles of cancer cells in the secretions of the lung, of the stomach, urinary tract, and other body secretions.

Since the beginning, there has been considerable skepticism and even antagonism to the vaginal-smear method. It has been asked, "What's wrong with the biopsy?" The surgical biopsy has been proved to be a reliable method of diagnosis. Even so, there has been no appreciable diminution in the death rate in uterine cancer in the last twenty years despite improvements in radiological and surgical techniques. Most gynecologists agree that the visualization of an early cervix cancer in clinical practice is an extreme rarity. Therefore, the early phase in the history of this disease is preclinical. The vaginal smear is adding an abundance of evidence to prove this concept. Papanicolaou,[2] Meigs,[3] Jones, Neustaedter, Mackenzie[4] and others have reported cancer cells found in vaginal secretions in women whose cervices exhibit clinical benignancy. In the past, biopsies have only been taken on cervices which exhibit a suspicion of malignancy. Unfortunately, it is still true that most gynecologists do vaginal smears only on cases where the cervix bleeds or looks suspicious. Most of them have not yet reached the stage of ordering them on the normal-appearing cervix; yet from this group come the most dramatic finds.

*Presented at the New York Academy of Medicine, Section on Obstetrics and Gynecology, Oct. 27, 1948.

Graham,[5] Foote,[6] Seibels,[7] and numerous other authors have reported the diagnosis of many early cancers by finding cells in the vaginal smear. Some of these have even been shown to be in a preinvasive or "carcinoma in situ" stage.

The Papanicolaou test offers its greatest contribution to the gynecologist in diagnosis and control of cervix cancer. Novak,[8] Te Linde,[9] Howard Taylor, Jr.,[10] and others have stated that squamous cancer has its origin in the squamocolumnar junction of the cervix. Walter Schiller,[11] who with the Schiller test has studied many early cervix cancers, goes so far as to state that 100 per cent of epidermoid carcinoma arises from the squamous margin of the squamocolumnar junction. If this is true, it means that cancer arises from a known spot no larger than a dime with greater frequency than from any other similar area in the human anatomy. Therefore, a method of sampling the squamous cells in this area periodically offers, first, a means of cancer control through early diagnosis while the lesion is still in a curable stage. Perhaps of equal significance is the fact that study of the cells in this region may throw further light upon the stage of cancer when it is in the process of becoming cancer.

One of the modifications of the Papanicolaou method is the "surface-biopsy" technique.[12] This may be defined as a scraping with a small wooden spatula of the squamous cells from the circumferential margin of this tissue at its junction with the gland epithelium of the cervix. The scraping gives a selective sample of cells removed prior to exfoliation. The cells are fresh and well preserved, and since their origin is known, a more definite interpretation may be made.

For the evaluation, clinical photographs are submitted of a number of examples of preclinical cancer of the cervix. These photographs of the cervices indicate the absence of any clinical lesion recognizable or even suspicious of a carcinoma. These are examples of early squamous cancer of the cervix where the cancer is developing invisibly on the exposed vaginal portion of the cervix at the squamocolumnar junction. They are not hidden from view in the endocervix. In all of these cases the early cancers were detected by the surface-biopsy scraping and these photographs were taken in the operating room immediately before surgical biopsies were secured for confirmation of diagnoses. Some of the clinical data may be of interest to demonstrate the importance of the cervical scraping as a method of selecting the cervix which may require multiple or serial biopsy sections to arrive at the true tissue diagnosis.

CASE 1.—Mrs. B., aged 43 years, had no symptoms of carcinoma, although recent menstrual periods had been somewhat prolonged. The cervix showed a benign parous appearance with residual chronic cervicitis and visible Nabothian follicles. Vaginal smears on this case failed to demonstrate abnormal cells. It was apparent from the clinical picture that no ulceration had yet developed and that the squamous tissue appeared to be intact. At this early stage the accelerated exfoliation associated with friability and necrosis of cancer tissue has not yet developed. Scraping, however, with the cervical spatula removed organized clusters of cells whose morphological character gave the cytologist a clear-cut diagnosis of carcinoma of the squamous type. Subsequently, biopsies were secured from both the anterior and the posterior lips. Those from the anterior showed benign cervicitis. Those from the posterior revealed a small but infiltrating squamous carcinoma.

CASE 2.—Mrs. K., aged 32 years, complained of leucorrhea. Clinically, the cervix showed a moderately large circular erosion, a fairly common picture found in parous women. Undoubtedly, the routine treatment in this case prior to the days of the vaginal smear would have been to do an electrocauterization. There was nothing to incite suspicion to call for a biopsy, and further, if biopsies had been taken, it would have been a major problem to determine in which segment of the large squamocolumnar circumference (measuring 5 cm. in

diameter) to obtain biopsies. The value of the scraping technique is well demonstrated in this type of case. A single circumferential scraping from the squamous margin revealed great clusters of cancer cells and of cornified cells, giving a clear-cut cytological picture of squamous cancer. It is a significant point frequently observed by us in securing scrapings from the preclinical cancers, that in this early preulcerative stage the scraping does not usually injure the malignant zone sufficiently to induce bleeding from the site, in marked contrast to the well-known behavior when a friable clinical cancer is traumatized. This case demonstrated the need for most careful and adequate sectioning of tissues to obtain pathological confirmation. After seventy-nine sections had been cut from four segments of the squamocolumnar junction, the diagnosis of carcinoma was not yet established. Only after an additional thirty sections were cut was the nest of squamous carcinoma found.

How early in the history of cancer may a diagnosis be made? Is there such a thing as a "precancer" or cancer precursor stage? Is the transformation of the cell from a benign to a malignant state a gradual or rapid transformation?

Much of the basic knowledge of cancer learned to date has been acquired through the study of the pathology of tissues obtained by biopsies, but biopsies were usually excised only in the presence of advanced and clinical disease. Recent studies suggest that by focusing the light of existing knowledge upon the individual cell, more may be learned concerning the change in that cell from a benign to a malignant type. Studies of cells scraped from the cervix under all possible environmental conditions, i.e., in good health, under conditions of acute, subacute, and chronic inflammation, in the presence of erosions, or leucoplakia, or ulcerations, promise to open a new world of understanding of cellular response to gynecological disease processes.

It has been stated by Traut[13] that the vaginal smear represented the most important single diagnostic test in the armamentarium of the gynecologist. We are in hearty agreement with him, and, indeed, feel too that to the student of cancer the opportunity for study of the inflammatory, hormonal, and other environmental changes which may influence the cell may best be afforded by the utilization in the hands of the experienced cytologist of the surface-biopsy modification of the Papanicolaou technique.

After studying many thousand samples of cells from the cervix in normal cases, in inflammatory lesions and malignant lesions, it has been found possible to make an attempt to sort out the different cell types on the basis of the nuclear and cytoplasmic morphology of the cell stained by the brilliant Papanicolaou stains and other more recently developed staining methods.

Four types of cells may be recognized. By far the great majority of cells sampled in this region exhibit the morphology of normal benign cells. Another group of cases may be placed in the category of inflammatory hyperplasia. Then a third group exhibits the morphology of malignant cells as described by Papanicolaou. We may often diagnose a cancer as a preinvasive lesion by the appearance of the cells in the scraping. The surface-biopsy scraping, however, has revealed what we visualize to be a fourth type of cell midway between the inflammatory and the malignant and exhibiting certain similarities to both. While the changes in these cells are not sufficiently marked to indicate to the cytologist that they are cancer cells, he nevertheless is impressed with the conviction that if they are not a malignant type of cells, they are the next thing to it. Similarly, a pathologist studying a doubtful biopsy from the squamocolumnar region may see a picture which he feels to be very close to a cancer, yet there is insufficient evidence to enable him to call it cancer. Frequently, in such cases, if more sections are cut a small cancer will be found. In others, even with serial sections, no cancer is found and the most extreme pathological

picture remains that of a borderline lesion. This is the case type under discussion today. Is there a transition phase, a real "stepping-stone," as Novak has described, "between the benign and the malignant"? The great James Ewing has stated, "It is not true that a pathological condition must be either cancer or not cancer. It may be neither one nor the other. It may be in the process of becoming cancer." The surface-biopsy scraping gives a very sensitive evaluation of a trend to cancer morphology in squamous cells developing in the circumferential margin of the cervix. Are we justified in calling these transitional cell types "precancer" cells? Is there such a thing as a "precancer" cell? We do not presuppose to be able to answer this question or to prove that the cells shown are precancer cells, but certain evidence will be presented which tends to suggest that we are studying a type of cell which is related to the formative stage of cancer. Those who have studied only with the use of the simple aspiration from the vaginal pool may not find familiarity with this cell type except as an occasional atypical cell finding. Our studies have indicated that accelerated exfoliation is not the rule at this stage and adequate concentrations of these cells may best be obtained by a surface-biopsy scraping technique. Only by having an adequate collection of these cells in the microscopic field is it possible to attempt any interpretation of such cells.

May I emphasize again that the majority of precancer cell findings have been detected in cervices exhibiting a benign appearance. Therefore, in the past, biopsies have been taken most infrequently, but the surface scraping has revealed concentrated collections of these cells, which have impressed us with their character as being a transitional type of cell on the border line between an inflammatory and cancerous change. These squamous cells have been described by us as the "precancer cell complex." The following morphological features have been observed to constitute this complex:

1. A persisting high concentration of cornified cells in the cervical scraping. The cytological picture is that of a continuous estrogenic or regenerative phase, the cornification level corresponding with the usual maximal level found at midcycle (preovulatory).

2. Atypical or "precocious"* cornified cells (Figs. 3, 4, 5).

3. Cell giantism (Fig. 1).

4. Abnormally large hyperactive and immature nuclei with hyperchromatic staining, and frequent cytoplasmic granules (Fig. 5).

5. Multilobulation and multinucleation in nuclei of all strata of the squamous layer, deep (Fig. 7), middle and superficial (Fig. 2).

6. Hyperplastic basal cells (Fig. 7).

7. Perinuclear "halo" frequently noted in superficial cell types (Fig. 6). This halo has been observed commonly at the expected time of ovulation. Possibly some hormonal alteration with the cell at this stage of development may account for this morphological phenomenon found in inflammatory as well as in early malignancy cases.

Many of these cells show evidence of a degree of immaturity. The surface cells show "precocious" cornification and accentuated keratinization. Comparative studies on the cornification process of squamous cells of the oral cavity compared to those of the vagina indicate certain similarities in the precancer cells of the cervix to those observed in oral leucoplakia. W. Burton Ayre, who has been conducting these comparative studies, states that in leucoplakia of the tongue, the disorder seems to have important systemic etiological factors and, due to the lack of some nutritional or hormonal factors, the intrinsic cell dy-

*A term originated by Dr. Robert Chambers.

namics concerned with the maturation and cornification process do not operate in the usual manner, and cornification and keratinization of the cell occur at an earlier than usual stage. Certainly, in the cervix many of the superficial cells show indications of disorder in the cornification process in cancer and in precancer. Certain environmental factors may be determined concerning the cells involved in this stage of cancer. There is usually some evidence of chronic

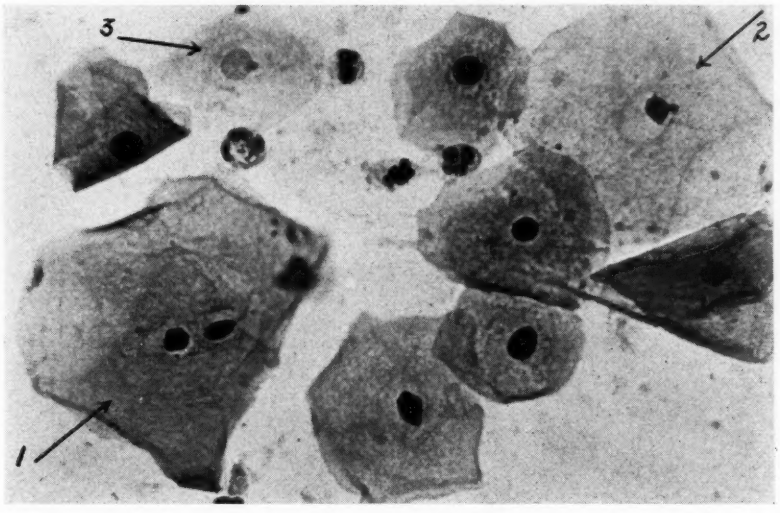

Fig. 1.—Precancer cell complex. Group of superficial cornified cells with atypical features. Large cell (No. 2) is a typical example of a normal, mature, cornified cell. All cells in group, except No. 3, show acidophylic staining. No. 3 is basophylic and shows lighter staining. Observe giant double-nucleated cell (No. 1.).

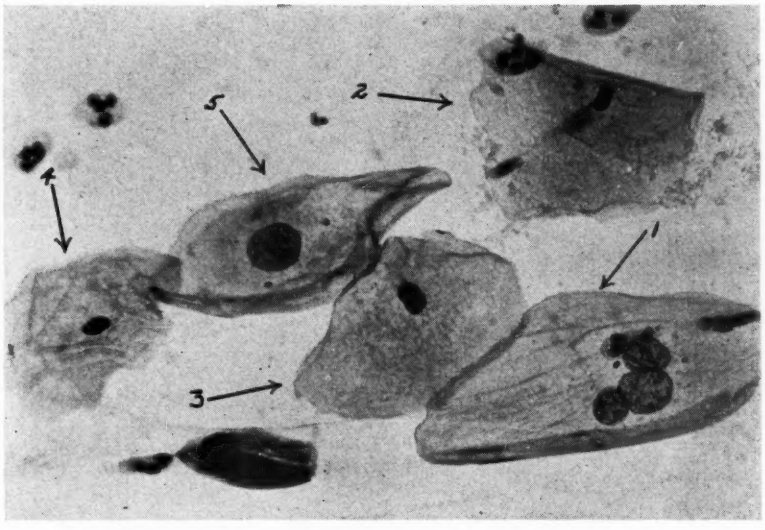

Fig. 2.—Precancer cell complex. Superficial cells showing atypical cornification. Observe multinucleation in cell No. 1. All cells show acidophylic (cornified) staining. Cells 2, 3, and 4 appear normal, while cell No. 5 has an abnormally large nucleus.

cervicitis involving the glands of the endocervix (Neisser). There is a concentration of cornified cells in the region of the squamous margin. There is a limited amount of evidence to suggest deficient excretion in these patients of thiamine and riboflavin, which may be linked with the finding of persisting high cornification (an index of impaired estrogen metabolism).

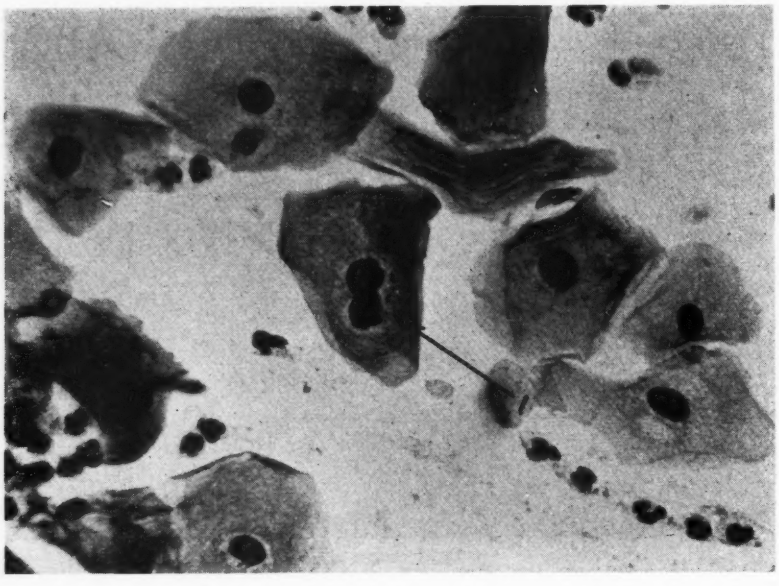

Fig. 3.—Precancer cell complex. Atypical cornification. Observe dumbbell-shaped nucleus (No. 1) and abnormally large hyperchromatic nuclei in most of the surface cells.

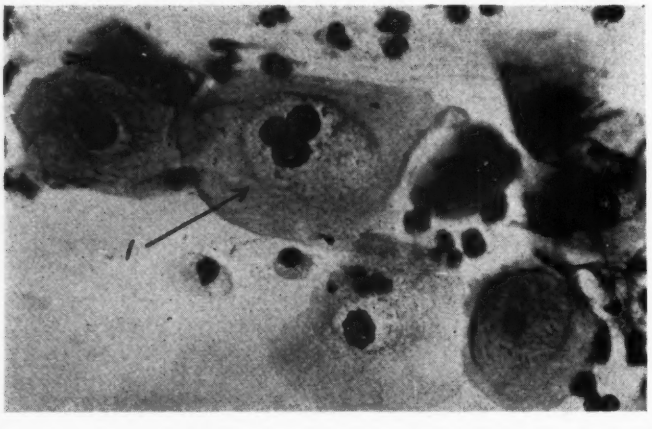

Fig. 4.—Precancer cell complex. Observe tri-lobate nucleus in surface cell which shows acidophylic staining reaction. Such cells have been termed "precocious cornified cells," a characteristic of the precancer state.

Brief mention should be made here of the clinical and cytological findings in various acute and subacute inflammatory states of the vaginal tract. These studies would tend to favor some etiological relationship between inflammation and cervical cancer. In the acute and subacute stages of trichomonad infestation

or a specific Neisserian infection, the purulent or mucopurulent secretions contain squamous cells exfoliated in great profusion from the exudative tissues. As the infection undergoes resolution, the vaginitis clears and finally the cervix resolves with a diminution or disappearance of the purulent secretion coinciding with clinical resolution. The endocervical glands are the last part of the vaginal tract to undergo resolution, and a chronic focus of infection remains in the vulnerable racemose glands centering around the squamocolumnar region. During

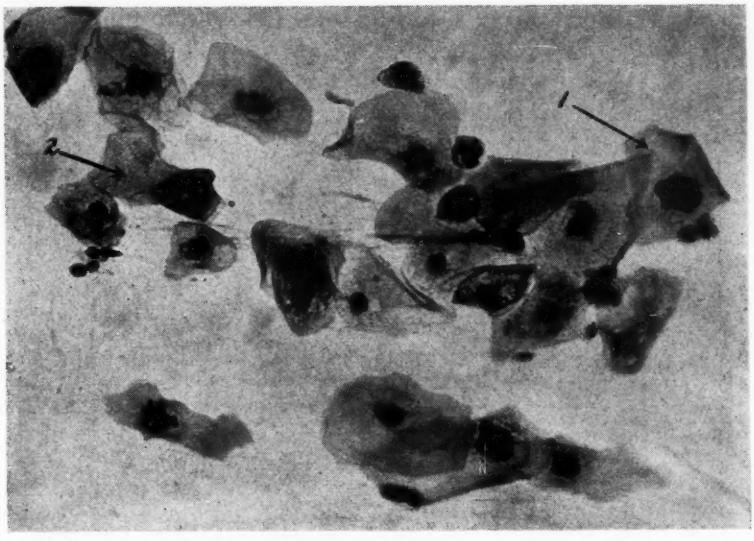

Fig. 5.—Precancer cell complex. Group of surface cells showing nuclear irregularities and hyperchromatic staining features characteristic of the precancer cell complex. All of the cells in this group show acidophylic staining of the cytoplasm. Note the large irregular hypertrophic nuclei in cells of types No. 1 and No. 2, examples of precocious cornification.

Fig. 6.—Precancer cell complex. Perinuclear halo well marked in several cells of this group. Note also large size and deep staining of the nuclei.

the acute phase, studies of the cells in the purulent vaginal secretion show nuclear and cytoplasmic changes, the nuclei showing an indistinct diffuse staining reaction with generalized enlargement of nuclei. Some degree of nuclear multilobulation may be noted. The cytoplasm shows a tendency to a diffuse indistinct

acidophilia simulating cornification but referred to as pseudo-cornification. It will be seen that these cells seem to represent a steppingstone between normal cells and the cell described as a "precancer cell." A neophyte in cytological interpretation may readily confuse these inflammatory cells with precancer or even with cancer cells. There are definite differences, however, which tend to suggest that the precancer state is something more than an inflammatory state. Although prolonged chronicity may be one of these factors, undoubtedly something else would appear to be added before a definite precancer or cancer status may develop. The frequency of precancer cell findings is roughly similar to that of cancer.

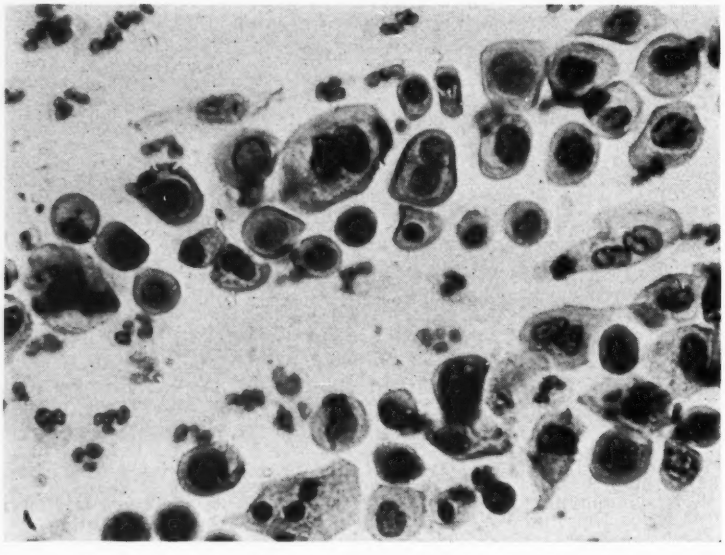

Fig. 7.—Precancer cell complex. Hyperplastic basal cells. Observe numerous binucleated cells and multilobulated nuclei.

Clinically, most of the precancer cases show no visible evidence of inflammation or of growth. Some show a minimal chronic cervicitis or an erosion, but these are common findings with cells of normal nuclear character. Vaginal smears on many precancer cases are negative except for an occasional atypical nucleated form. Cervical scrapings from the squamocolumnar junction, however, reveal concentrations of cells with the following features not shared by inflammatory cells.

1. The nuclei exhibit a greater deviation from normal with exaggerated multilobulation.

2. The staining shows a clear-cut definite picture in both the cytoplasm and the nucleus.

3. The nuclei show hyperchromatic staining approaching that of cancer cells. Selective staining achieved by the Papanicolaou stains appears to be an important diagnostic feature.

4. These precancer cells arise only from this one area, the marginal circle of squamous tissue, and marked exudation is usually not present.

5. Immediately adjacent to the precancer zone, concentrations of mature morphologically normal cornified cells are found, though in some cases there is found an admixture of pseudo-cornified (inflammatory) cells.

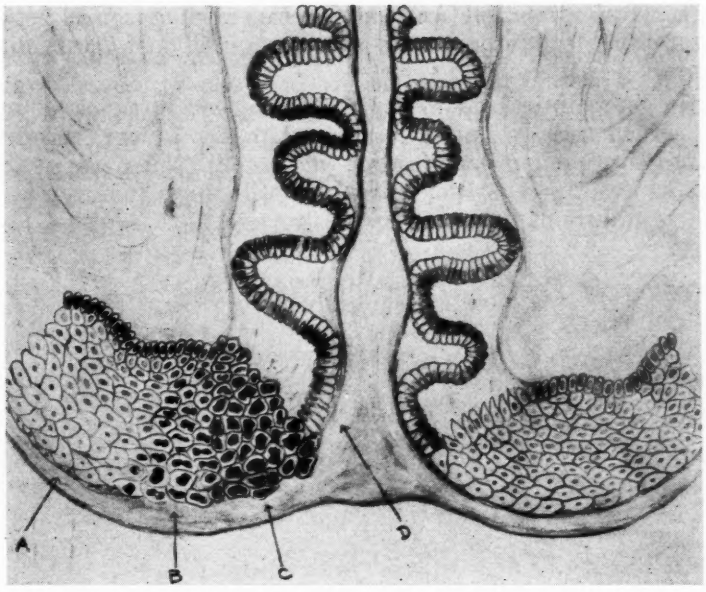

Fig. 8.—Diagrammatic representation of architecture of cervix. Observe squamocolumnar junction, the site where squamous carcinoma originates. Note normal squamous cells (A), borderline or precancer cell types (B), and cells of malignant morphology (C). D represents the cylindrical endocervical epithelium. While in the fixed surgical specimen the squamocolumnar junction assumes an endocervical position, in the physician's office eversion with a bivalve speculum causes the junction to assume an ectocervical position where the vulnerable cells are readily accessible to the cervical scraping.

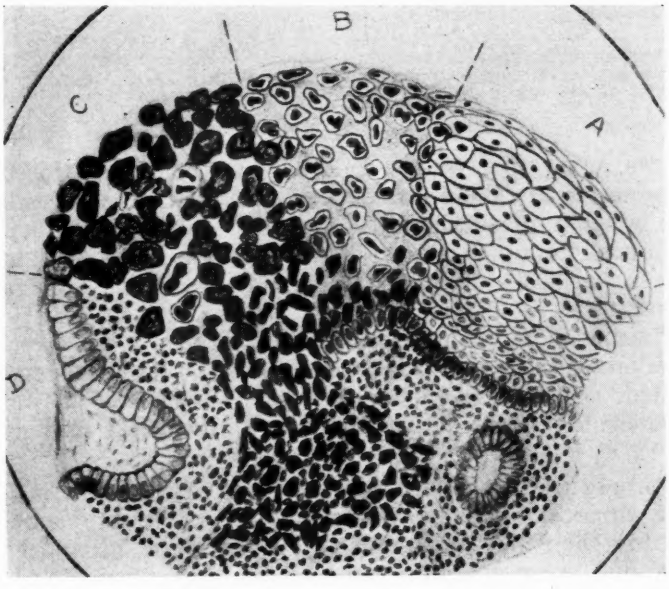

Fig. 9.—Diagrammatic representation of a high-power view of squamocolumnar region in early carcinoma. The cancer zone is represented by (C). Note anaplasia, hyperchromatism and early evidence of invasiveness. Immediately adjacent to the cancer zone is the precancer zone (B), where cells of the precancer complex type are found. Normal squamous cells, with cornified elements along the surface, are found in zone (A). D represents zone of glandular epithelium of endocervix.

It is important that a differentiation be made between a routine vaginal smear and a cervical scraping. Accurate precancer diagnosis is dependent upon the surface-scraping technique as the dilute vaginal pool is unreliable for the demonstration of precancer cells.

In the early preclinical microscopic stage of cervix cancer a concentration of normal cornified cells is found peripheral to the cancer. Approaching the cancer, cells with precocious cornification are noted. These are of the precancer type. Then the cancer cells themselves are still more immature, and usually exhibit complete failure of the cornification process.

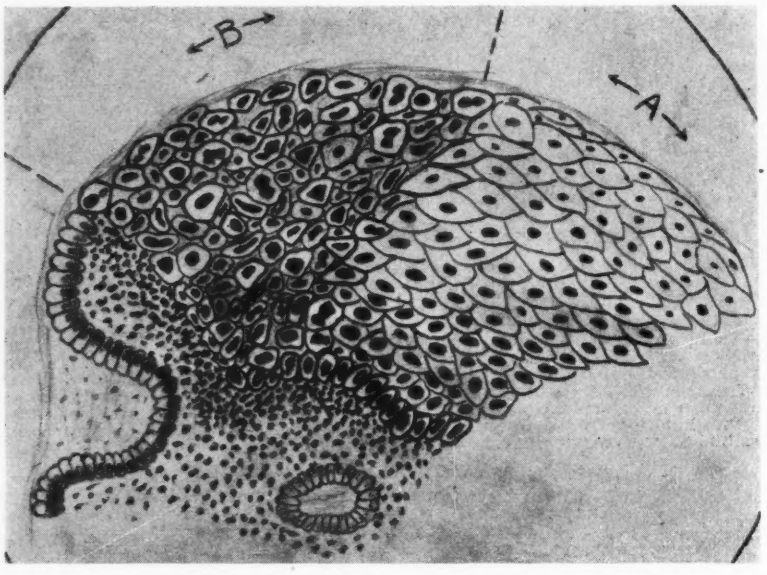

Fig. 10.—Diagrammatic representation of squamocolumnar region in true precancer cell complex case. The surface-biopsy scraping in these cases fails to show cancer cells, but shows clusters of the cells of precancer type and many cornified elements from the adjacent normal epithelium (A).

How are we going to evaluate these cells? The first procedure is to do adequate biopsy studies. These have usually revealed an interesting and puzzling picture in which hyperplasia and a degree of anaplasia are evident with the same atypical nuclei found extending from the base up to the surface. These lesions have been variously diagnosed as secondary squamous hyperplasia, precancer, hyperkeratosis, anaplasia, and some border into the entity called intraepithelial carcinoma or carcinoma in situ. Prophylactic therapy in most cases demands conservative removal. Such cases, once the lesion is removed, may no longer be studied. Premature or radical surgery is hardly justified and surely the importance of the problem warrants careful clinical and cytological observation.

The next procedure in the evaluation of this cell complex is to study their behavior. The surface-biopsy technique enables us first to detect these cases and then to study their subsequent progress. Do these lesions regress and the precancer cells disappear spontaneously, or do they persist and become progressive, developing into carcinoma? At the present preliminary stage of our knowledge, investigation of behavior has been inadequate to provide any degree of certainty. However, some contributory observations have been made in individual cases which were followed closely. It has been asked, "Is this a normal

healing proliferative cell?" Healing erosions don't show them, even after cauterization.

First, let us consider reversibility. While many cases exhibiting inflammatory hyperplasia have been observed over a period of months to regress and disappear, this spontaneous regression has not been observed in the precancer complex cases. Some of these have been followed without surgery for one to three years. In these, the precancer cell type has persisted, while in five untreated patients progression to carcinoma (verified by tissue study) has been noted. Several of these will be discussed briefly.

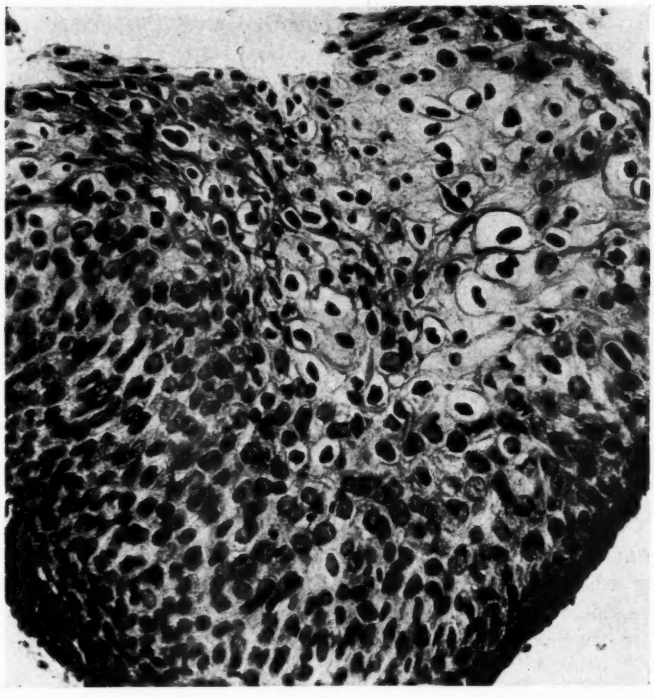

Fig. 11.—Cervical biopsy from squamocolumnar region in the type of case represented in Fig. 10. Observe many atypical and multiobulated nuclear forms throughout this tissue; yet serial sections failed to show evidence of genuine carcinoma. This tissue shows the origin of the atypical precancer cells found in the cervical scrapings.

PRECANCER CASE 1.—One of the cases studied was that of a sister of one of our technicians, a nulliparous woman, aged 29 years, complaining of irregular menstrual bleeding. The cervix appeared normal. Vaginal smears revealed a persisting high cornification of the regenerative phase peak without evidence of ovulation. Cervical scrapings revealed cells of the precancer complex. Clinically, this patient showed no progression over the course of a full year. The lesion was not treated locally or removed by surgical biopsy. Cytologically, the cells became more active in appearance. A ring biopsy of the squamocolumnar circle was performed with the cone-knife[14] and following serial sections a lesion diagnosed as intramucosal carcinoma at the squamocolumnar junction was found. At this stage its rate of growth would appear to be slow. Only two mitotic figures were detectable in serial sections of the entire noninvasive growth. This patient had no further treatment than complete excision with the cervical cone-knife followed by electro-conization and subsequent vitamin B therapy. For a year following the operation, the patient showed normal cervical scrapings. She is now pregnant and continues to show normal cytology. Of course, she will be kept under close observation, having careful cytological examinations for some years.

While evidence reported by Te Linde, Pund, Taylor, and others indicates slow progression in many preinvasive cervix carcinomas to an invasive and clinical stage over a period of several years, there is evidence too that different cancers may and do progress all too rapidly.

PRECANCER CASE 2.—Mrs. L, 40 years of age was curetted for bleeding in December, 1947. Her first cytology test was diagnosed four months later as "precancer." Two months later it was still reported as "precancer." She was kept under observation and developed intermenstrual bleeding which prompted a return to her gynecologist and this time, four months later and nine months since the first test, a third cytology scraping was taken. The cytological diagnosis was positive for cancer cells, and a ring biopsy with serial sections was required to reveal this cancer as an early invasive lesion. While, undoubtedly, some lesions may persist in a precancer and in a preinvasive cancer stage for many months or years, this lesion was already launched on its invasive career, and presumably soon would have become a clinical ulcerating malignant growth.

PRECANCER CASE 3.—Mrs. L, aged 28 years, was picked up in routine screening in Clinic. An initial diagnosis was made of "precancer" cells. Subsequent follow-up four months later showed cells of cancer type in her surface-biopsy smears. While pathological opinions vary on the lesion, most call it either preinvasive cancer or early invasive cancer. The lesion showed marked mitotic activity suggestive of rapid progression.

PRECANCER CASE 4.—Mrs. W, aged 42 years, with a diagnosis of precancer, was studied at three-month intervals with an unchanging picture for eighteen months. Finally she began to have menorrhagia and some irregular bleeding. Although the resident took a single biopsy on this case, the tissue studied was negative and radium was inserted. The patient is still being followed. We feel that adequate biopsy study would have revealed the origin of the abnormal cells. This case perhaps contributes little except that the patient showed persistence of the abnormal cells.

PRECANCER CASE 5.—The case of Mrs. J, 39 years of age, was diagnosed by cell smears mailed from Montana. The first cell scraping was diagnosed as precancer. Six months later a repeat cytology was diagnosed cancer. Biopsy with serial sections was advised. Dr. Hawkins of Helena, Montana, could see no cancer, but did a circular amputation of the cervix, and sent the entire specimen to us to do serial sections. The tissue showed early invasive cancer.

PRECANCER CASE 6.—Mrs. B., aged 48 years, had an initial diagnosis of precancer cell complex and six months later of carcinoma. The patient was admitted to hospital and the resident took a single surgical biopsy which proved to be negative. Although this patient has not since returned to our clinic, attempts are being made to secure additional cytological and tissue studies.

PRECANCER CASE 7.—The case of Mrs. P, aged 36 years, was detected by routine surface-biopsy and diagnosed as precancer. Three months later a repeat scraping was diagnosed again as precancer. Three months later a repeat scraping showed cancer cells (six months after the first test). Multiple biopsies were needed to locate lesion diagnosed as early invasive cancer by our pathologists. At this early stage, this cancer did not exhibit friability and bleeding when scraped with the spatula.

Experimental therapy to patients showing precancer cells has to date yielded certain information, mostly of a negative type. For example, certain cases were studied to determine whether large doses of vitamin B complex may cause disappearance of the cells in the smear. This has not been found to be true. Similarly, diopterin, teropterin, penicillin, sulfanilamide, testosterone, and progesterone have all been tried with negative results. Very promising preliminary results have been obtained by combining massive doses of the

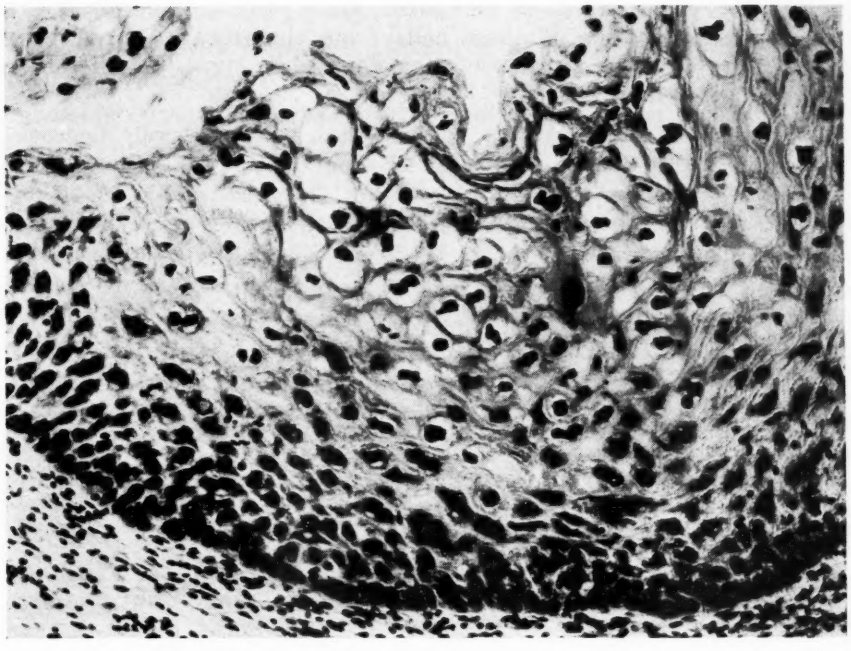

Fig. 12.—Cervical biopsy showing cells of precancer type in tissues. This section of tissue was adjacent to an area showing actual squamous carcinoma.

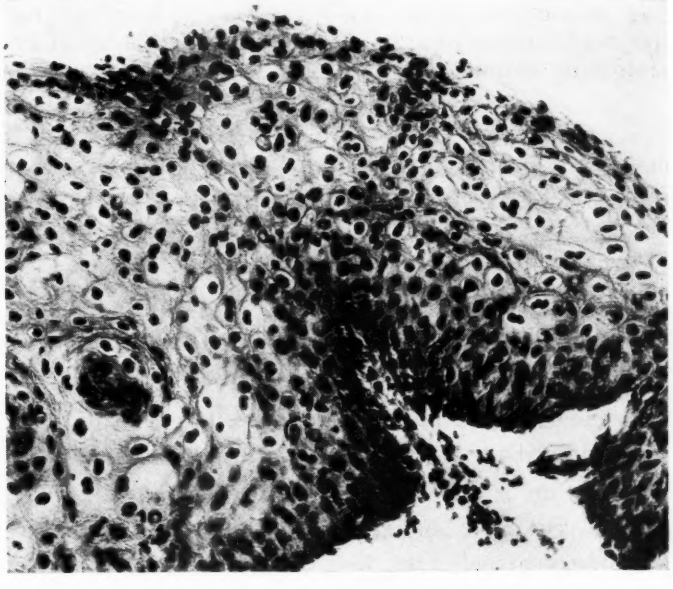

Fig. 13.—Cervical biopsy from the squamocolumnar region in another case showing many cells of the "precancer-cell complex" type. Throughout the tissue no further evidence of carcinoma was demonstrable in following thorough biopsy studies.

estrogenic hormone with large doses of riboflavin. While no change was observed after four to six weeks of treatment, more prolonged administration was followed by disappearance of these cells from the smears. Four cases have shown the same response. Only brief mention will be made here of these studies which are in a preliminary stage.

One of these cases, that of Mrs. L, aged 31 years, was cytologically diagnosed as precancer cell complex. The patient was treated for four months with a massive dosage of an estrogen combined with a heavy dosage of riboflavin. The precancer cells finally disappeared and could no longer be detected in the surface-biopsy smear. Following the cessation of the hormonal therapy, withdrawal bleeding was persistent, and while a curettage was performed a ring biopsy was also obtained for tissue study of the squamous tissue at the junctional area. The tissue showed no evidence of abnormal growth. Of course, it must be admitted this case was diagnosed initially by cytology and did not have an initial biopsy. It was felt that a biopsy might have removed the entire growth.

Such isolated case studies provide inadequate but still provocative evidence that we are dealing with a very early stage in the history of cervix cancer, using a method permitting study of cellular response and behavior. Statistics have been found difficult to collect or evaluate at the present early stage, although a few comparative figures are presented.

Variation has been noted in different selected groups, for example, in the in-hospital and gynecological clinic group of 1,300 patients, forty-five precancers have been diagnosed during an interval when thirty-six cervix cancers were found. (It should be explained that this includes patients referred to the cancer clinic as well as those attending the free gynecological clinic.) The average age of the precancer group is 40.8 years, while that of our cancer patients was 46.8 years.

In another outside (screening) group the incidence was lower. In 2,318 cases, sixty-four precancers were "called" to one hundred cancers. (High cancer incidence was accounted for on the basis that many of these tests were mailed to us as definite suspects.)

Summary

Papanicolaou's vaginal smear technique has been described as a major advance in uterine cancer diagnosis. A modification of this technique, the surface-biopsy cervical scraping has been found especially useful in preclinical cancer by enabling evaluation of growth potentialities in the cells of the squamous margin of the squamocolumnar junction. Cells scraped from this vulnerable zone are described and classified into four groups: normal, inflammatory, precancer cell types, and cancer cells.

The precancer cell complex, a group of cells of borderline nuclear morphology, has been described and representative photomicrographs presented.

Behavior studies on a selected group of cases showing cells of precancer type are presented. Seven cases are briefly presented. Six cases showed progression from a precancer cell type to a cancer cell type over periods varying from six to eighteen months. In five of these, the lesions terminally were confirmed by surgical biopsy. One case showed cells of precancer type without progression, persisting after eighteen months. No case of spontaneous regression to normal was observed during this time.

Experimental therapy to precancer cases has been attempted. A group of cases is presently under observation. One of those is described in whom precancer cells disappeared following prolonged administration of massive doses of an estrogenic-riboflavin combination.

Diagrammatic representation of the localization of cancer cells, precancer cell types, and normal cells in early microscopic cancers is attempted.

The cytological method is visualized as opening up a valuable new field of approach for diagnosis and for behavior studies of lesions believed to represent the formative stage of cancer.

The author wishes to express sincere appreciation to Dr. Robert Chambers and Dr. W. Burton Ayre for assistance in the interpretation and evaluation of cells classified as of precancer type; to Dr. J. S. Henry and Dr. W. A. G. Bauld and other Staff Members of the Department of Gynecology and Obstetrics of the Royal Victoria Hospital, who have cooperated in making possible the careful follow-up on cases diagnosed as precancer. Appreciation is due also to Miss Evelyn Dakin, Director of Technicians, and to the entire Technical Staff who have cooperated in the preparation of this work.

This work was assisted by a grant from the Public Health Foundation for Cancer and Blood Pressure Research, New York.

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MacFarlane, Catherine, Sturgis, Margaret C., and Fetterman, Faith S.: Control of Cancer of the Uterus, J. A. M. A. 138: 941, Nov. 27, 1948.

The authors report their findings on 732 volunteers who have been examined more or less regularly over a period of 10 years. Eight cancers of the pelvic organs were discovered in the group of 732 volunteers over this ten-year period. The authors continue to stress the importance of periodic pelvic examination, especially on women past 30 years of age who have had one child. WILLIAM BERMAN.

Department of Reviews and Abstracts

Selected Abstracts

Cesarean Section

Pedvis, S., Irwin, J. K. L., and Philpott, N. W.: Fetal Mortality and Morbidity in Cesarean Section, Surg., Gynec. & Obst. 88: 103, 1949.

The authors have attempted an analysis of infant mortality in 353 cesarean sections with 357 infants resulting. The operations were performed in three different periods: from July 1, 1940, to Dec. 31, 1949; from July 1, 1944, to July 1, 1945; and from Jan. 1, 1946, to Dec. 31, 1946. These three periods were chosen in order to study three different types of anesthesia: namely, general, spinal, and local. The infants were classified as normal (those who were perfectly well both at birth and discharge); morbid (those who required prolonged resuscitation or had respiratory difficulties during the first twenty-four to forty-eight hours); and dead (nonviable infants, stillborn infants, and infants who died shortly after birth). The gross fetal mortality in this series was 7.3 per cent and the morbidity 11.2 per cent; 36.6 per cent of the deaths were due to prematurity, while 29.3 per cent were caused by atelectasis. A statistical analysis of the deaths in the different anesthetic groups is attempted. There seems to be no statistical difference in the number of infant deaths in the various anesthetic groups. However, such an analysis appears invalid, because of the varied and uncontrollable maternal complications which contributed to the deaths. Similarly, an attempt is made to determine statistically the influence of the various types of premedication in the causation of infant death. Statistically, there is no difference. Moreover, such statistical analysis is again invalid for the reason mentioned above. A special type of management for cesarean section babies is suggested and an attempt made to justify such management statistically. There is no statistical difference between the group submitted to special management and that without special management.

L. M. HELLMAN.

Shaw, Wilfred: Vaginal Operations for Cystocele, Prolapse of the Uterus, and Stress Incontinence, Surg., Gynec. & Obst. 88: 11, 1949.

The author describes in detail the anatomical relations of the endopelvic fascia in the vicinity of the anterior vaginal wall. There is a condensation of the endopelvic fascia behind the urethra. At operation no precise plane of cleavage is found between the vaginal and vesical fascial layers. In the operations used by the author for cystocele, prolapse, and vaginal hysterectomy, this fascia (which he terms the "post-urethral ligament") plays a most important part. In the operation for cystocele, the bladder is freed in the usual manner, the posturethral ligament is then brought down and sutured to the anterior surface of the cervix, the rest holding up the bladder. This key suture is also used in the Manchester-Fothergill operation. In vaginal hysterectomy, the ligament is used to support the anterior portion of the peritoneum, as well as the round ligaments on either side. Stress incontinence is treated by utilizing a sheet of fascia lata as a sling beneath the urethra. The two ends of the sling are brought up through holes bored in the pubic bone and sutured anteriorly. At the time of publication the author had treated twenty-five patients in this manner with satisfactory results.

L. M. HELLMAN.

Endometriosis

Kelly, Francis J., and Schlademan, K. Ramsay: Endometriosis, Its Surgical Significance. A Critical Analysis of 79 Cases, Surg., Gynec. & Obst. **88:** 230, 1949.

During 1,991 consecutive abdominal gynecologic operations, the authors encountered 79 histologically verified cases of endometriosis. These represent the basis of this paper. Acquired dysmenorrhea was present in 48.2 per cent of the cases, while dysmenorrhea of increasing severity was present in 33.5 per cent. One of the most striking features of endometriosis is its relation to fertility. Using a normal fertility rate of 88 per cent, the authors found that the absolute fertility rate for the series under consideration was 46.4 per cent. Though radical operative procedures were considered necessary in the majority of these cases, the authors felt that conservatism was justified when possible as indicated by an absolute fertility rate of 23.7 per cent after conservative surgery. L. M. HELLMAN.

Extrauterine Pregnancy

Karsh, Jamil: Abdominal Pregnancy Following Rupture of Cesarean Scar, Canad. M. A. J. **60:** 70, 1949.

A young secundigravida, previously delivered by cesarean section, developed term labor lasting about three days, followed by five weeks of diffuse abdominal pain, which gradually subsided. Vaginal bleeding appeared in the third week, and persisted for two months. Thereafter, she had regular menses for eight months, followed by irregular vaginal bleeding and discharge, with low grade sepsis, for four months. At laparotomy, the degenerating ovum was surrounded by a thick adherent fibrous capsule. The uterus was of normal size, with a gaping ruptured cesarean scar. Hysterectomy was done. IRVING L. FRANK.

Gynecology

Muellner, S. Richard: The Etiology of Stress Incontinence, Surg., Gynec. & Obst. **88:** 237, 1949.

In a previous study the author made an attempt to determine the lesion responsible for stress incontinence by examining ninety-five patients with exertional incontinence and forty-five continent multiparas using cystometry, cystoscopy, cystography, and urethrography. These studies all failed to revealed a specific lesion. During the past year eighty-five observations have been made using a fluoroscopic technique, thirty of these on women suffering from stress incontinence. These studies were carried out with the bladder filled with a contrast medium of 5 per cent sodium iodide to which 20 c.c. of aqueous Diodrast had been added. Usually 200 to 250 c.c. of the solution were sufficient. Observation was then made through the fluoroscope with the patient standing and supine. Care was always taken to maintain the relationship of the x-ray tube and the symphysis so that changes in the position of the bladder resulting from change of posture could be accurately evaluated. Spot films were also taken from time to time. In the normal nullipara, while recumbent, the bladder has a smooth outline. When she coughs, the base of the bladder does not yield, but the impulse on the increased intra-abdominal pressure is dissipated along the dome and the sides of the bladder. When she is asked to void, the base of the bladder can be seen to descend sharply so that the region of the internal sphincter becomes the most dependent portion and assumes a pointed appearance. This is the first important maneuver in the complex process of micturition. It is this descent of the internal sphincter which opens it slightly and permits a small amount of contrast medium to enter the proximal urethra. If such a subject is asked to inhibit the urinary stream, she pulls the base of the bladder up to a level slightly higher than it had assumed before micturition. In a continent multipara, the events are very similar except that the bladder is somewhat larger and flabbier and the bladder supports more yielding. In the continent multipara, coughing

and straining will initiate some descent of the internal sphincter but the sphincter itself being in good tone no urination occurs. In the incontinent individual relaxation of the pubococcygeus muscle allows the base of the bladder and the internal sphincter to descend during each period of coughing or straining. With some slight relaxation of the sphincter, the descent of the bladder is enough to initiate urination. L. M. HELLMAN.

Ball, Thomas L., and Javert, Carl T.: Fertility and Dysgerminoma Ovarii, J. Clin. Endocrinol. 8: 694, 1948.

This communication briefly reviews the literature in which pregnancy associated with or following dysgerminoma of the ovary is discussed. In the largest series of cases tabulated by Seegar the fertility rate was 23 per cent.

A case is reported in which a 39-year-old primigravida was delivered by midforceps of a male infant weighing 2,900 Gm. Examination of the infant revealed a first degree hypospadias, there were no other abnormalities noted.

The patient herself gave a history of having been operated upon twelve years earlier and, at that time, a right salpingo-oophorectomy was done for a solid tumor of the right ovary. Postoperatively, four x-ray treatments were administered. The exact dosage was not determined; however, it was stated that the left ovary was protected with a lead screen. Since the patient did not cease to menstruate after the radiation therapy, the amount of radiation that reached the left ovary was not enough to cause castration. The slides from the original tumor were reviewed by the present authors and the diagnosis of dysgerminoma was clearly established. A plea is made for conservatism (unilateral oophorectomy when only one ovary is involved) in cases of dysgerminoma in spite of the anaplastic character of the tumor.

HERBERT J. SIMON.

Menstruation, Dysmenorrhea

Davis, M. Edward, and Fugo, Nicholas W.: The Cause of Physiologic Basal Temperature Changes in Women, J. Clin. Endocrinol. 8: 550, 1948.

It is now generally accepted that the basal body temperature in the normally menstruating woman is biphasic in character. In this communication the authors have made studies to determine the cause of this phenomenon. An analysis of well over 1,000 temperature graphs showed that 75 per cent of patients present a curve which, when properly interpreted, will give exact information as to the time of ovulation. Emotional, physical, and metabolic stimuli in themselves cause irregular temperature fluctuations in the remaining 25 per cent and thus mask the normal curve.

In a study of one hundred basal temperature graphs of women who conceived, seventy-two were known to have had coitus at least once during the period of the temperature rise or at its peak. It is thought that the high level of the temperature during the luteal phase of the cycle is caused by progesterone. The fact that the authors were able to recover from the urine increased amounts of pregnandiol during the period of elevated temperature supports this view. Twenty-four to thirty-six hours prior to the onset of the menses, the activity of the corpus luteum ceases, the pregnandiol levels drop, and the temperature curve returns to the preovulatory level. If pregnancy occurs there is no drop in temperature, whereas in an anovulatory cycle, there is no rise in temperature. All this substantiates the theory that progesterone is the cause of the temperature shift. The authors were able to bring about a typical temperature rise in two groups of young women without ovarian activity. In the first were four young women with primary amenorrhea, and the second included four young women who had been subjected to surgical castration and hysterectomy for pelvic disease. In both these groups the method employed was a daily oral dose of 0.3 mg. of ethinyl estradiol. Then, at the end of about two weeks, 10 mg. of progesterone in oil were administered intramuscularly daily in ad-

dition to the ethinyl estradiol, for twelve to fifteen days. The only variation from the temperature curve of normal women was that there was a more abrupt rise and a slower fall of the temperature. In a group of twelve women, the ovarian function following surgical removal of the uterus was studied. Cyclic elevation of the temperature associated with increased pregnandiol excretion was found. It would, therefore, appear that the uterus is not essential for a normal hormonal cycle.

In order to explain the fact that conception often occurs during a temperature rise, it is suggested that the theca-interna cells excrete progesterone prior to actual ovulation. It may, therefore, be postulated that ovulation takes place during the temperature rise rather than, as was formerly believed, just before the rise. HERBERT J. SIMON.

Buxton, Charles L., and Atkinson, William B.: Hormonal Factors Involved in the Regulation of Basal Body Temperature During the Menstrual Cycle and Pregnancy, J. Clin. Endocrinol. **8**: 544, 1948.

In this communication the actual cause of the temperature rise during the latter half of the menstrual cycle and the progress of the basal body temperature during pregnancy are presented.

Six patients with secondary amenorrhea and lack of ovarian function as determined by endometrial biopsy were selected for study. A temperature base line was established and then a priming dose of estrogen was given daily for about two weeks. Immediately thereafter 10 to 25 mg. of progesterone were administered daily from seven to fourteen days. The estrogen produced a slight depression of the basal temperature whereas the progesterone caused a rise up to a degree or more. Endometrial biopsies confirmed hormonal activity. The postovulatory temperature rise in normally menstruating women can be maintained by the administration of large amounts of chorionic gonadotropins. It would appear that the chorionic gonadotropin stimulates the corpus luteum to produce progesterone which in turn causes the rise in temperature. To prove that chorionic gonadotropin is not directly responsible for the maintenance of the temperature rise, an equivalent amount was given, after estrogen priming, to a 31-year-old bilaterally ovariectomized woman. No rise in temperature resulted.

It would be expected that the elevated body temperature would continued throughout pregnancy since there is an apparent increasing amount of progesterone as determined by the pregnandiol excretion. Three patients kept temperature charts throughout their period of gestation. In each case there was a gradual drop of the temperature to the preovulatory levels during the fourth month. To explain the discrepancy between the apparent rise in the progesterone as indicated by the increase in pregnandiol excretion and the fall in temperature, it is predicated that a refractory state develops in which the thermogenic action of the progesterone is overcome by thermodepressant factors. A second theory suggests that a lytic activity of the trophoblast on the decidual tissue of the mother during the early months of pregnancy results in a slight febrile response. An additional explanation to account for the fall in basal body temperature as pregnancy progresses assumes a diminished physiologic activity of the progesterone.

HERBERT J. SIMON.

Brown, Willis E., Bradbury, J. T., and Jennings, A. F.: Experimental Alteration of the Human Ovarian Cycle by Estrogen, J. Clin. Endocrinol. **8**: 453, 1948.

This study was undertaken in order to demonstrate any alteration in the human menstrual cycle caused by the administration of estrogen. The corresponding ovarian cycle was followed by weekly endometrial biopsies.

In the first series of six normal patients, a single dose of 20 mg. of stilbestrol was given early in the menstrual cycle (fourth, fifth, or sixth day). The result was prolongation of the interval to thirty-eight days. In this group of patients, the intervals before

and after treatment averaged twenty-nine to thirty days. In all cases but one, endometrial biopsy showed secretory endometrium just before the onset of the period.

A group of five women complaining of dysmenorrhea was similarly treated. The 20 mg. dose of stilbestrol did, however, cause an anovulatory cycle in one patient. The authors conclude (with previous workers) that a single large dose of estrogen given early in the menstrual cycle will delay but not inhibit ovulation and thus increase the length of the cycle.

Another group of five dysmenorrheic women was given stilbestrol over a period of thirty days, beginning at the end of the period. One mg. of stilbestrol was given daily for the first ten days, 2 mg. daily for the second ten days, and 3 mg. daily for the third ten days. Anovulatory bleeding occurred usually three days after the last dose and the patients were relieved of their painful menses. This was continued for three successive cycles without apparent ill effect.

In a final series of six patients, stilbestrol was given in the postovulatory phase of the cycle. The luteal phase was not prolonged, the progestational endometrium was normal, and there was no increase in the length of the cycle. It would thus appear that the human corpus luteum, once formed, is not affected by the administration of estrogen.

HERBERT J. SIMON.

Macpherson, Cluny: Pelvic Allergy, Canad. M. A. J. 60: 54, 1949.

Excellent, and sometimes dramatic, results are reported with the use of Adrenalin chloride hypodermically (1 c.c. of 1:1000 solution), as emergency treatment in cases of severe functional dysmenorrhea. Recently the author has used Benadryl (50 mg.) to be taken thrice daily on the premenstrual day, with good results in preventing menstrual pain.

IRVING L. FRANK.

Miscellaneous

Waksman, Selman A., and Lechevalier, Hubert A.: Neomycin, a New Antibiotic Active Against Streptomycin-Resistant Bacteria, Including Tuberculosis Organisms, Science 109: 305, March 25, 1949.

The authors report a new antibiotic produced by *Streptomyces faradiae.* The organisms are grown on a medium containing nitrogen, carbohydrates, and salt. The antibiotic is easily removed from the medium and concentrated by methods previously developed for the isolation of streptothricin and streptomycin. It has been termed by the authors Neomycin, and is a basic compound most active in alkaline solution. It is soluble in water and insoluble in organic solvents and thermostable. It has proved active against numerous Gram-positive and Gram-negative organisms, and especially the mycobacteria. The antibiotic spectrum of crude Neomycin is distinct from streptomycin and streptothricin. It is particularly active against streptomycin-resistant bacteria and possesses considerably more activity against *Mycobacterium tuberculosis.* It has limited or no toxicity in animals. Neomycin has not yet been obtained in crystalline form and therefore little can be said concerning its chemical nature.

L. M. HELLMAN.

de Soldenhoff, Richard: Early Ambulation in Obstetric and Gynaecological Cases, Lancet, p. 961, Dec. 18, 1948.

The author discusses his experiences with early rising in 1,611 obstetric and 212 gynecologic cases. Puerperal women are permitted to sit up in bed six to eight hours after delivery, and are allowed out of bed with lavatory privileges on the third postnatal day. A two-step platform is provided to reaccustom patients to stair climbing. Cesarean patients follow the same routine. The now familiar advantages of this regime are described.

IRVING L. FRANK.

Newborn

Chapman, Earle M., Corner, G. W., Jr., Robinson, David, and Evans, R. D.: The Collection of Radioactive Iodine by the Human Fetal Thyroid, J. Clin. Endocrinol. 8: 717, 1948.

This study corroborates the theory that the human fetal thyroid probably begins to function at about four and one-half months.

Radioactive iodine was administered to nine pregnant women who were to be operated upon forty-eight hours later for the termination of pregnancies which endangered their lives. It was found that the thyroid tissue of 7- to 12-week fetuses exhibited no radioactivity. In those aged from 14 to 32 weeks, the radioactivity tended to increase with increasing age. Histologic studies suggested that the onset of thyroid function is associated with the appearance in the gland of definite follicles containing colloid.

From this study it would appear that toxic goiter in pregnant women may be treated by radioactive iodine up to the fourth month of pregnancy without effect on the thyroid of the fetus. HERBERT J. SIMON.

Norman, R. M.: Cerebral Diplegia Following Birth Injury, Bristol Med.-Chir. J. 65: 43, 1948.

In nine cases of cerebral diplegia a detailed examination of the brain was made. All of these nine patients were firstborn and eight were boys. There were two twin births. In four cases the birth weight was low, 4½ to 5½ lb. The birth was rapid in two of these cases and precipitate in one case. In one case there was dry labor with a postmature infant; in another, the mother was known to have a pelvic contracture. In every case the birth history was abnormal or suggestive of intracranial damage. Three infants showed severe asphyxia; two showed apathy with inability to take the breast; three had twitching of the limbs during the first few days of life. During life, six of these patients had a symmetrical spastic paresis of the limbs with contractures of hamstrings and adductors and signs of upper neurone deficiency; two had a hemiplegia with contractures and a less severe spastic paresis of the leg on the opposite side; in one case there was rigidity of the extrapyramidal type with associated athetosis. Epilepsy developed in six cases. The lesions found at post-mortem examination were of two main types: (1) lesions of the cerebral cortex which were attributable to hemorrhage from or stasis in veins draining into the superior longitudinal sinus; (2) lesions of the central white matter of the brain and basal ganglia often symmetrically placed which were attributable to hemorrhage or circulatory stasis in areas drained by the tributaries of the great vein of Galen. HARVEY B. MATTHEWS.

Pregnancy, Complications, Toxemia

Gordon, Charles A., and Rosenthal, Alexander H.: The Expectant Treatment of Placenta Previa. A Study of 50 Maternal Deaths, Surg., Gynec. & Obst. 88: 259, 1949.

In a study of 1,011 maternal deaths occurring in Brooklyn in the ten-year period from 1937 to 1947, 145 were officially assigned to hemorrhage. Placenta previa was associated with deaths in fifty instances. In these fifty cases of placenta previa, twenty-five patients were delivered pelvically, while twenty-two were delivered by cesarean section. The major cause of death was infection, which occurred in eighteen cases. Hemorrhage was responsible for death in fifteen cases, while rupture of the uterus occurred eight times. The pattern of hemorrhage showed considerable variation in time of onset, amount of initial hemorrhage, and character of recurrent bleeding. Initial profuse antepartum hemorrhage occurred twelve times; spotting for four or five weeks followed by moderate or

profuse hemorrhage three times; recurrent slight bleeding for one to four weeks followed by moderate, profuse hemorrhage fifteen times; recurrent slight bleeding for four weeks to four months followed by moderate profuse hemorrhage seven times; initial moderate bleeding followed in one to six weeks by second moderate to profuse hemorrhage seven times; one episode of bleeding in the seventh month, once. The first instance of hemorrhage occurred during labor five times. The authors feel that vaginal or rectal examination should not be performed in the home nor in suspected cases should it be done in the hospital until one decides to terminate the pregnancy at about the thirty-eighth week. Tamponade and dilating bags are obsolete and version nearly so. Interference from below should be restricted to simple rupture of the membranes or, in case of a frank breech in a multipara, an easily accessible limb may be pulled through the cervix. Great care should be taken with the placental stage of delivery, with a view to prompt manual removal if placental bleeding should continue. Finally, the authors feel that the expectant treatment of placenta previa is safe under proper conditions. They emphasize, however, that the patient should remain in the hospital during the period of expectancy.

L. M. HELLMAN.

Switzer, Paul K., and Fouche, Heyward H.: The Sickle Cell Trait: Incidence and Influence in Pregnant Colored Woman, Am. J. M. Sc. 216: 330, 1948.

The authors differentiate clearly between sicklemia in which there is sickling of the red cells but no blood destruction or increased rate of regeneration, and true sickle-cell anemia in which there is sickling as well as active blood destruction and increased regeneration as evidenced by reticulocytosis and nucleated red cells. There are numerous reports in the literature of true sickle-cell anemia associated with pregnancy; however, there have been no studies made of the occurrence of pregnancy in patients with sicklemia nor of the effects of pregnancy on such patients. Five hundred consecutive Negro women who were pregnant were examined for sickling. In addition, two hundred fifty nonpregnant Negro women of childbearing age and two hundred fifty Negro men were also studied. There was an incidence of sickling of approximately 14 per cent in all three groups. The sickling trait did not interfere with conception nor had it any apparent deleterious effect on either the pregnancy or the labor in any of the pregnant women. One patient had active sickle-cell anemia of a mild type. It was not known whether this existed prior to her pregnancy. In twenty-two patients with sicklemia studied in the hospital, the pregnancy did not initiate a blood-destructive process.

HERBERT J. SIMON.

Pregnancy, Physiology

Black, Elinor F. E.: Diuretic Effects of Estrogens in the Last Four Months of Pregnancy, Canad. M. A. J. 59: 431, 1948.

The author presents a series of forty cases of excessive weight gain in pregnancy, 77.5 per cent of which responded satisfactorily to the administration of small doses of estrogens. The author divides weight gain in pregnant women into three groups: those who go through the nine months with a normal weight gain; second, those who gain weight rapidly with onset of edema and later develop hypertension and albuminuria; and third, those who gain excessively throughout pregnancy despite restrictions in diet, salt and fluid intake, yet develop no edema and no other evidence of toxemia. The administration of estrogens as a method of limiting excessive weight gain during pregnancy is apparently free from deleterious effects on the patient and the fetus. Twenty-nine of the forty patients showed a satisfactory response to estrogen therapy. Five patients showed a poor response. Two patients showed an added weight increment during the course of estrogen therapy. It is felt that the clinical results that have been observed suggest that further investigation and assessment of the role of the estrogens in the matter of fluid retention are warranted.

WILLIAM BERMAN.

Puerperium

Norrish, R. E.: Residual Dilatation of the Upper Urinary Tract Following Pregnancy, Practitioner **161: 47, 1948.**

It has long been recognized that there are changes in the form of the renal pelvis and ureter during pregnancy, although the cause of these changes is still a matter of discussion. These changes are associated with urinary stasis and predisposition to infection, as shown by the frequent occurrence of pyelitis in pregnancy. In uncomplicated cases return to normal form and tonus of the ureter and bladder occurs about the sixth week after delivery. This may be delayed by the presence of infection, and there may be some degree of residual dilatation. This residual dilatation may be maintained by subsequent pregnancies until the ureter becomes stiffened by fibrosis and the pelvis atonic, a condition that may persist after the childbearing period. Four illustrative cases are presented (with pyelograms). In the first case, the ureters and renal pelvis returned to normal by the eighth week after delivery. In the second case only the right ureter was dilated during pregnancy and there was no infection; the condition cleared up completely. In the third case the patient was 52 years of age; she had had six children; pyelitis had occurred in her first pregnancy and recurred in each subsequent pregnancy. For many years after her last pregnancy she continued to have backache, dysuria, and increased frequency; and examination showed a coliform urinary infection. Intravenous pyelography showed the right ureter and pelvis dilated, with kinking and twisting of the ureter, as is often found in pregnancy. In the fourth case the patient had had two pregnancies, with the urinary infection during the first pregnancy, which had persisted intermittently. During an exacerbation of symptoms, intravenous pyelography showed the right renal pelvis and ureter to be much dilated. When she became pregnant again a few months later, pyelograms showed dilatation of the ureter and pelvis on both sides. Four months after delivery the left ureter and pelvis were normal, but dilatation persisted on the right side and urinary infection was still present. HARVEY B. MATTHEWS.

Boyd, David A., Jr., and Brown, De Witt W.: Electric Convulsive Therapy in Mental Disorders Associated With Childbearing, J. Missouri M. A. **45: 573, 1948.**

Most mental disorders associated with childbearing occur after delivery and are characterized by manic-depressive and schizophrenic reactions. Experience with electroshock in major psychoses (nonpuerperal) indicate that it is most effective in cases with a strong depressive trend, less effective in manic patients, and least beneficial in schizophrenia. A review of the cases reported in literature of puerperal psychoses treated with electroshock, and the authors' own experience indicate that the same is true in the puerperal psychoses. The fact that electroshock has proved effective in a large percentage of cases of puerperal psychosis may be attributed to the fact that many of these psychoses show a strong depressive trend. While some therapists consider that electroshock treatment should not be given during the first month after delivery, other therapists have found that the prompt use of electroshock therapy is markedly effective and shortens the duration of the illness. In the authors' cases of postpartum psychosis, psychiatric indications for electroshock therapy have been the deciding factors as to whether it is to be used and when it is to be given. As soon as routine psychiatric and physical examinations have been completed, and electroshock has been found to be definitely indicated, this treatment is begun. In the authors' cases, therapy was instituted on the twenty-second, twenty-fourth, and fourteenth days after delivery, respectively. Two cases of puerperal psychosis are reported in which good results were obtained.

Manic-depressive and schizophrenic psychosis occurring during pregnancy are dangerous to both the mother and the child; delay of treatment of the psychosis until after the termination of the pregnancy may render the psychosis irreversible. Electroshock

therapy has not been found to be dangerous to the mother or to cause termination of the pregnancy, as shown by the cases reported in literature. It often makes it possible to carry the patient to term and at the same time to improve her physical as well as mental condition. The treatment is begun as soon as the diagnosis and the indications for electroshock therapy are established. Two cases of electroshock therapy during pregnancy are reported. In one of these cases the pregnancy was far advanced when treatment was begun in order to relieve uncontrolled excitement that threatened the lives of both the mother and the child; in this case the child was delivered prematurely, but lived and grew normally; the mother required further electroshock treatments in the puerperium, but made a complete recovery. HARVEY B. MATTHEWS.

Dunlap, John C., and Diddle, A. W.: Comparative Effect of Synthetic Estrogenic Substances on the Postpartum Breast, J. Clin. Endocrinol. 8: 880, 1948.

In this paper the effectiveness of dienestrol is compared with diethylstilbestrol and alpha estradiol in preventing engorgement of the postpartum breasts of nonnursing mothers. The authors' results show that alpha estradiol was frequently ineffective, whereas, with dienestrol and diethylstilbestrol, engorgement was more often averted. They further found that engorgement recurred less frequently after administering dienestrol than after diethylstilbestrol. None of the drugs used appeared to cause any increase in the lochia rubra. The authors call attention to the fact that breast engorgement and lactation are apparently independent of one another. The former is caused by lymphatic and vascular stasis, not by distention with milk. The flow of milk is stimulated more by suckling than by any hormonal action; hence, when it is desired to dry up the breasts, it is unwise to massage or empty them. HERBERT J. SIMON.

Items

Increase in Size of the Journal

Our readers are notified that, beginning with the January issue, the JOURNAL will be enlarged to a total of 232 pages of reading matter. See announcement on page 28 of the advertising section of this number.

Clinical Assembly

The Fifth Annual Midwinter Clinical Assembly in Obstetrics and Gynecology given by a group in Southern California will be held during the week of February 13 to 18, inclusive. For further information apply to

DR. GEORGE E. JUDD,
1930 Wilshire Boulevard,
Los Angeles 5, Calif.

Correspondence

Rh Sensitization

To the Editor:

In answer to many questions addressed to me, raised by an article on "Rh Sensitization in a Primipara Caused by Intramuscular Injection of Human Serum Resulting in Fatal Erythroblastosis" by Wallace, Wiener, and Doyle, published in THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, December, 1948, this unfortunate publication has confused and disturbed a considerable number of physicians, particularly obstetricians, several of whom have written me about it. The idea that *clear* serum or *clear* plasma may produce Rh sensitization when injected into a human being who is Rh negative, particularly a woman who subsequently bears an Rh-positive child, is not supported by careful analysis to date. This single case report is entirely unconvincing and I believe it has frightened both physicians and laymen quite unnecessarily.

It is known, and we have proved repeatedly in the Blood Grouping Laboratory of Boston, that even minute doses of whole blood or red blood cells, as little as one-tenth of 1 c.c., repeated on several occasions, may sensitize an Rh-negative individual. Between 50 and 60 per cent of our experimental group of Rh-negative males receiving such injections of Rh-positive cells eventually develop Rh antibodies. There is the possibility, therefore, that during the injection of serum or plasma if intact red cells are present in the liquid (which not infrequently occurs and in the past has not been carefully avoided) an Rh-negative person might receive a stimulating or sensitizing dose. However, if the plasma or serum is carefully prepared and no intact red cells are contained therein, there should be no concern about this possibility. We have tested the blood of several hundred Rh-negative men and women who have received both single injections and multiple doses of plasma intravenously and find no evidence of Rh sensitization in any of these to date.

In addition, we have verified cases of Rh-negative women who have begun developing Rh antibodies as early as the fifth week of gestation in a proved first pregnancy. We know from numerous tests that fetal blood contains Rh-positive red cells as early as the third or fourth week of gestation and, therefore, the possibility of transplacental sensitization from Rh-positive cells may exist in the Rh-negative women harboring an Rh-positive fetus even as early as the second month of gestation. In essence, therefore, it may be stated that the case report of Wallace, Wiener, and Doyle does not prove or even present a strong possibility that their patient was sensitized after an intramuscular injection of serum. Much more likely this was one of the rare patients in whom sensitization occurred due to pregnancy itself relatively early during a first gestation.

LOUIS K. DIAMOND, M.D.

300 LONGWOOD AVENUE,
BOSTON, MASS.
AUGUST 30, 1949

Reply by Drs. Wallace and Wiener

To the Editor:

The letter by Dr. Diamond is most helpful since it has given us an opportunity to clarify certain points in our article "Rh Sensitization in a Primipara Caused by Intramuscular Injection of Human Serum Resulting in Fatal Erythroblastosis."

1. While a single injection of compatible blood is sufficient to cause a rise in titer of *alpha* and *beta* antibodies, a minimum of two properly spaced injections is required to bring about Rh sensitization. Group O individuals already have a background of sensitization

against the A and B factors as evidenced by the alpha and beta agglutinins normally present in the serum. The injection of group A blood into such individuals, therefore, brings about an anamnetic specific reaction so that there is a prompt rise in the alpha antibody titer. The normal Rh-negative individual has no such background of sensitization and must first be primed by an injection of Rh-positive blood or a pregnancy with an Rh-positive fetus. After a latent period of about three to four months or longer, the primed Rh-negative individual can usually be made to respond to a second contact with Rh antigen by the production of Rh antibodies.

2. Sensitization of Rh-negative individuals by injections of Rh-positive blood is successful in more than half the cases. Sensitization of Rh-negative individuals by Rh-positive fetuses occurs on the average in only one out of fifteen to twenty cases. This is obviously a question of *dosage,* because much more blood is introduced by injection than could leak across a placental barrier.

3. The most sensitive test for the presence of Rh antigen in a substance is to inject it intravenously into a primed Rh-negative person. When an Rh-negative person has once been sensitized and a sufficient interval of time has been allowed to pass, even a minute dose of antigen will bring about a substantial rise in antibody titer. Based on such indirect evidence it has become clear that fetal red cells leak into the maternal circulation most regularly at parturition, though this may also occur at any time during the pregnancy, even as early as the seventh week as in our case report, which is the subject of the present discussion.

4. Since a minimum of three to four months is necessary to prime an Rh-negative individual, and since our patient showed antibodies as early as the seventh week of gestation it is obvious that she must have been primed some time before the pregnancy began. The only exposure that could be elicited in the past history was the injection of pooled adult serum received at the age of eight years.

5. Even serum prepared in such a way as to avoid trauma to the red cells will contain some stromata in suspension from effete red cells. Certainly there have been and probably still are in some parts of this country laboratories whose facilities do not permit the "proper" preparation of serum and plasma. Further, such serum prepared from pooled blood, outdated blood, and centrifuged blood will contain significant quantities of stromata, and therefore Rh antigen, from hemolysis due to intergroup reactions, aging, and trauma. No doubt, rare Rh-negative individuals exist who could be primed by even such small amounts of antigen. It is quite possible, of course, that our case is extremely rare or unique just like other rare cases of sensitization to poor antigens like Hr_0, hr", etc. In any event, its unusual features made it important enough to report.

6. Dr. Diamond's studies on sensitization of Rh-negative patients by plasma injections are important. For the results to be of significance, however, it is necessary to show that at least two plasma injections were given to each subject at an interval of not less than three to four months.

7. That the principle of priming followed by a latent period of three to four months is probably correct follows from our successful application of the principle for the preparation of Rh antisera. While we often succeed with only two injections, other workers who ignored this principle have had to use multiple injections up to sixty in number before obtaining results.

8. Even if our case is exceptional, it seemed important to point out that the injection of pooled plasma or serum is not as harmless as commonly assumed. Pooling of serum also increases the chance of transmitting the virus of hepatitis, and of inducing A-B sensitization, which can give rise to erythroblastosis. Obviously, therefore, the therapeutic use of human serum and plasma requires more intensive investigation from the standpoint of the hazards associated with such injections.

A. S. Wiener
J. T. Wallace

64 Rutland Road
80 Hansen Place
Brooklyn, N. Y.
November 16, 1949

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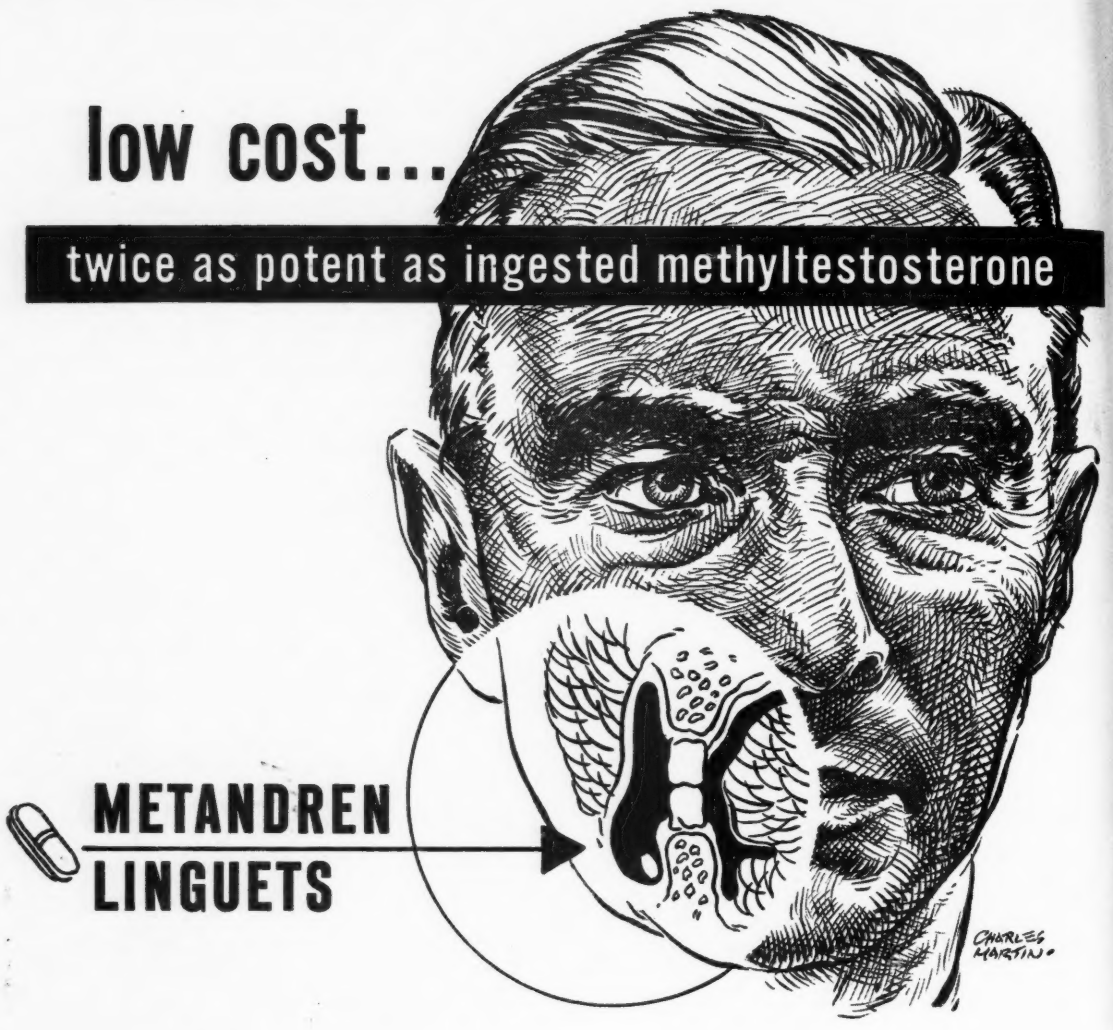

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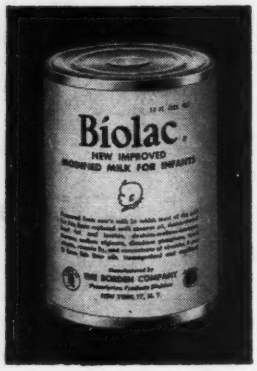

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